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Challenging diagnosis of a rare disease: hypophosphatemic osteomalacia – case report and literature review

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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 (P_i) 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.[1] Because of that the disturbance in its metabolism can cause symptoms from various organs, mainly the skeletal and muscular system.[2] 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).[3] 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.[4] The first case of tumor-induced osteomalacia was described by McCance in 1947. Until 2018 there have been reported about 500 cases of TIO wordlwide[4] and the number has risen significantly after that study, as in 2022 there have been conducted a systematic review indicating about 1700 cases.[2] Its prevalence varies by country.[5] 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.[6] Tumors producing FGF-23 can be located anywhere in the body in both bones and soft tissue what makes them hard to locate.[7] The symptoms of this condition are generalized weakness, diffused bone pain, frequent bone fractures, bone deformities, what causes functional impairment.[2] 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.[8]

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 od 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 inflamantory), 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.

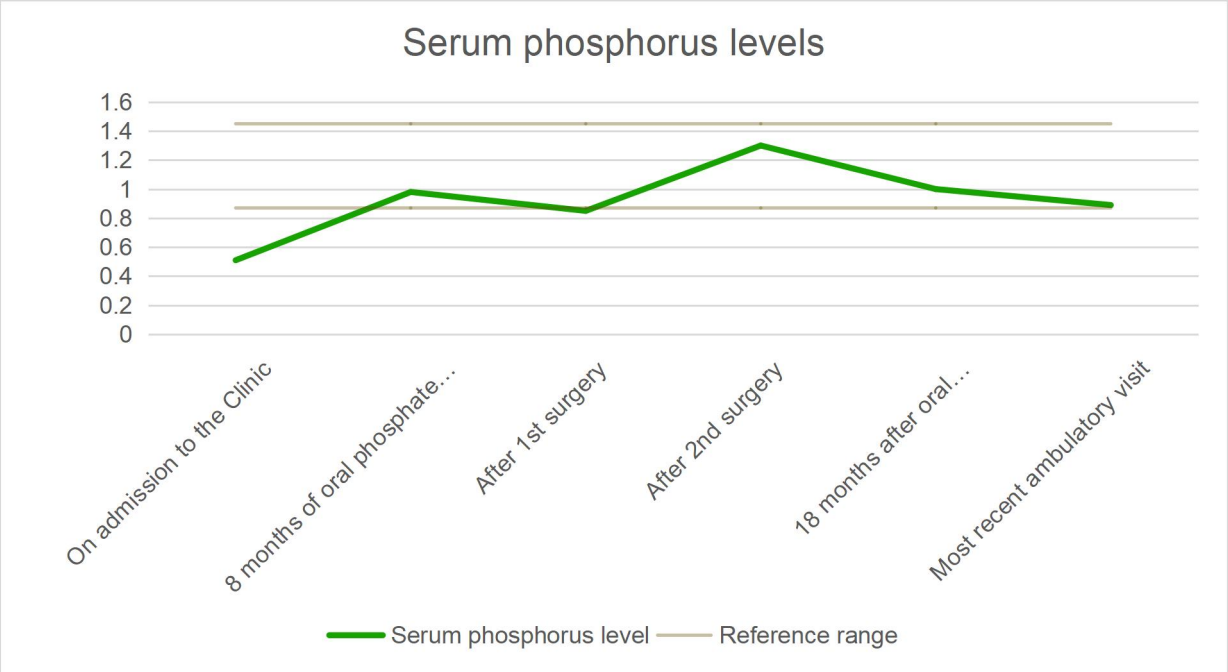

Figure 1. *Patient's phosphate levels over the course of treatment.*

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.[9]

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.[3]

Phosphate is retrieved from diet in the small intestine.[10] 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.[11] Other paths of maintaining the normal phosphate levels are its releasing from bones and regulation in kidneys in the proximal tubule.[12] The renal regulation of P_i is mediated by PTH and FGF-23.[13] If the serum P_i rises, secretion of there hormones is stimulated which reduces the expression of Npt2a and Npt2c in proximal tubules – transporters that are responsible for renal P_i reabsorption. This leads to increased urinary P_i excretion and lowers its serum concentration.[14] FGF-23 is secreted by osteoblasts and osteocytes what is stimulated by $1,25(OH)_2D$ and high P_i levels.[15,16] Another crucial organ in maintenance of phosphate management is parathyroid gland that not only responds to calcium and P_i serum levels but also is regulated by $1,25(OH)_2D$.[3,15] 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.[17]

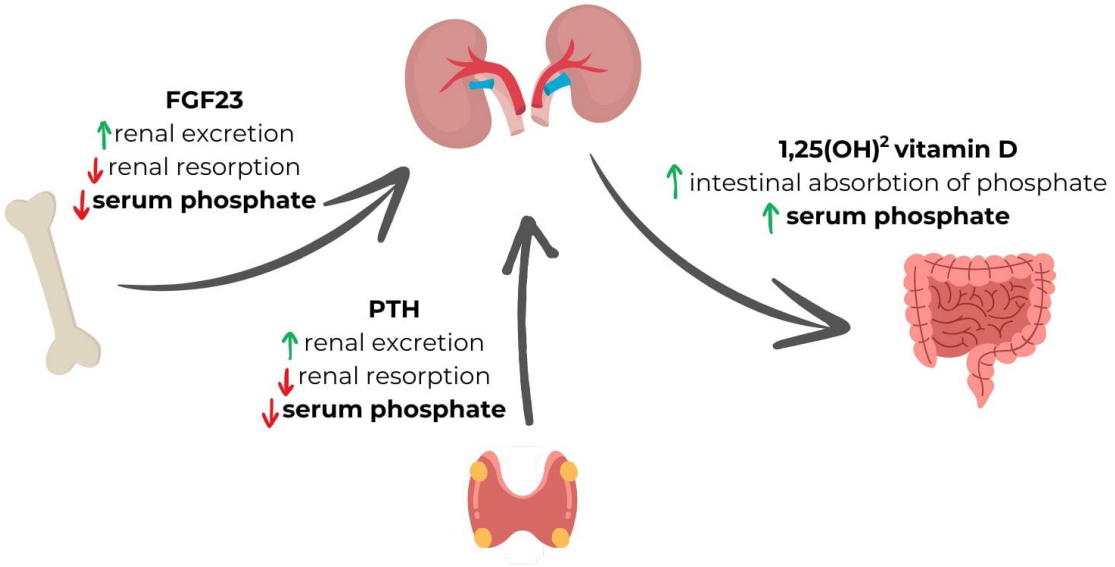

Figure 2. *Direct action of FGF-23, PTH and 1,25(OH)$_2$D in regulation phosphate homeostasis. 1,25(OH)$_2$D - 1,25-dihydroxyvitamin D; FGF-23 - fibroblast growth factor 23; PTH – parathyroid hormone. Source: adapted from Figure 2. Aljuraibah F, Bacchetta J, Brandi ML, et al.*[18]

Figure 3 shows the complexity of PTH, FGF-23 and 1,25(OH)$_2$D 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.

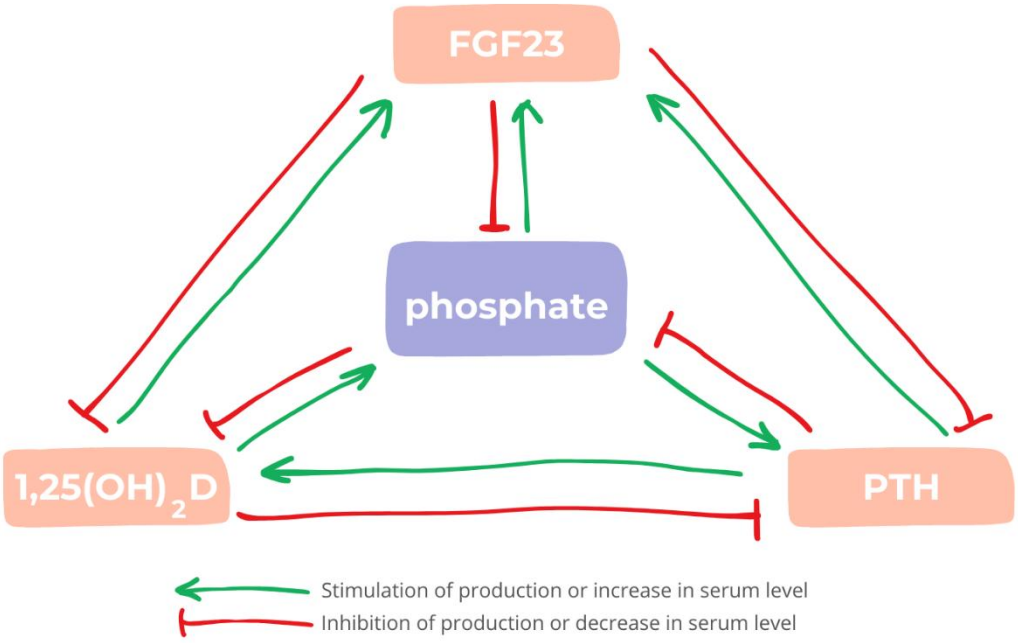

Figure 3. *Overviev of physiologic interactions between phosphate and its key regulators. 1,25(OH)$_2$D - 1,25-dihydroxyvitamin D; FGF-23 - fibroblast growth factor 23; PTH – parathyroid hormone. Source: adapted from Figure 2 Aljuraibah F, Bacchetta J, Brandi ML, et al.*[18]

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)$_2$D) and increases the 24-hydroksylaze (enzyme involved in degradation of 1,25(OH)$_2$D) 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).

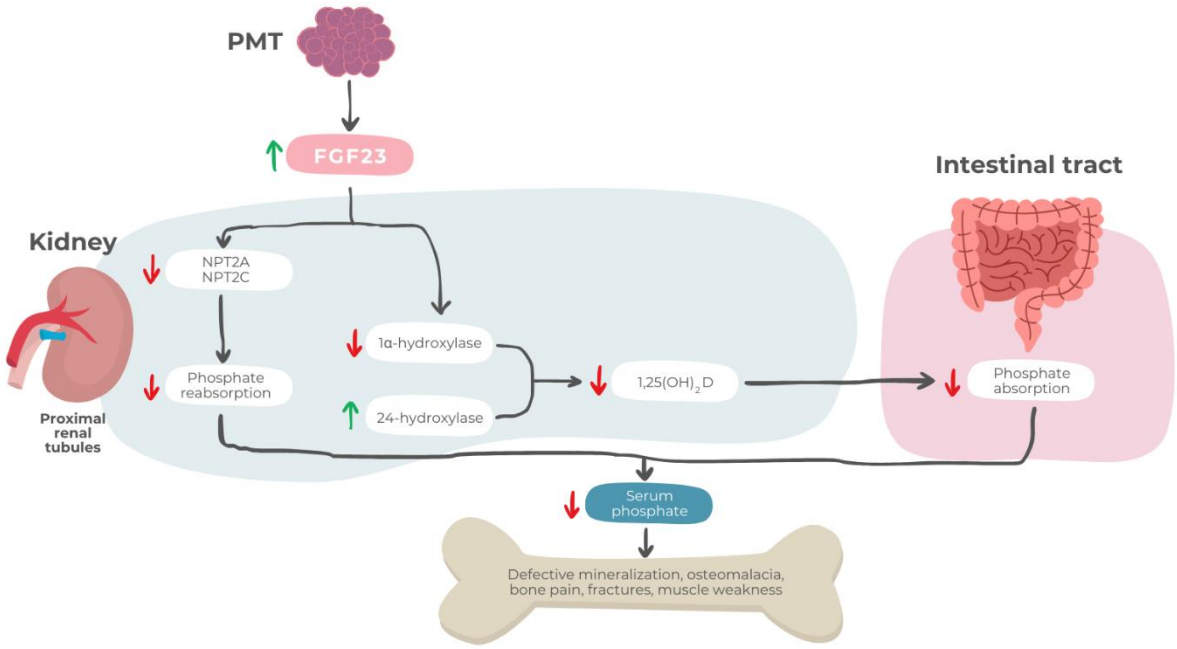

Figure 4. *Patophysiology of TIO. 1,25(OH)$_2$D - 1,25-dihydroxyvitamin D; FGF-23 - fibroblast growth factor 23; NPT2 - type II sodium phosphate contrnsporter; PMT - phosphaturic mesenchymal tumor. Source: adapted from figure 1 from Jan de Beur SM, Minisola S, Xia W bo, et al.* [21]

Diagnosis

Example causes of hypophosphatemia
1. Hypophosphatemia mainly caused by excessive renal excretion 1.1 FGF-23 mediated[22]

1.1.1 Genetic

- XLH[23]
- NF1[2425]
- Osteoglophonic dysplasia
- ADHR

1.1.2 Acquired

- chronic alcohol consumption and withdrawal[18]
- chronic intravenous iron supplementation therapy[2627,28]
- TIO

1.2 Non-FGF-23-mediated

- Renal Fanconi syndrome[29,30]
- Primary and secondary hyperparathyroidism

2. Impaired actions of vitamin D metabolites
   - Vitamin D deficiency[31]
   - Vitamin D metabolism defects
3. Malabsorption, malnutrition[32]
4. Transcellular shifts
   - Diabetic ketoacidosis
   - Hyperventilation
   - Refeeding syndrome
   - Respiratory alkalosis
5. Drugs
   - Aminoglycosides
   - Antiretrovirals[29,30]
   - Bisphosphonates
   - Catecholamines
   - Diuretics
   - Glucose or insulin infusion
   - Mannitol
   - Tetracyclines

Table 1. *Differential diagnosis of hypophosphatemia*[21]

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.”[18]

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.[33]

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). [34] 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. [21] 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). [21,35] 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. [21,36] Venous sampling of FGF-23 levels can be used to differentiate, localize or confirm a suspected tumor in functional imaging. [4,21 , 37] A typical finding in postoperative histopathological material is phosphaturic mesenchymal tumor (PMT) or mixed connective tissue tumors (MCT).[38,39]

Treatment

The primary and most recommended form of TIO therapy is its surgical removal with tumor-free margins.[21] If the tumor cannot be resected, ablative therapy in the form of using heat, cold, chemical agents or radiofrequency can be performed. [4] 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.[35] This form of therapy is also recommended in patients with identified tumor before the operation performance.[21] Also cow milk can be used as a source of oral phosphate.[40] However, using oral phosphate salts and active vitamin D can lead to side effects such as abdominal pain, diarrhea, secondary-tertiary hyperparathyroidism, hypercalciuria, nephrocalcinosis.[41] 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_2HPO_4 and NaH_2PO_4) and active vitamin D in increasing serum phosphate, TmP/GFR and $1,25(OH)_2D$, decreasing alkaline phosphate, improving osteomalacia. Berosumab is approved for patients with TIO in several countries.[21,35,42] 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.[21]

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.[21] Patients with hypophosphatemia have higher risk of glucose intolerance, obesity and other manifestations of the metabolic syndrome.[40] 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.[5] 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 Michalczewska 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.

References:

1. Ito N, Hidaka N, Kato H. The pathophysiology of hypophosphatemia. *Best Pract Res Clin Endocrinol Metab*. 2024;38(2):101851. doi:10.1016/J.BEEM.2023.101851
2. Rendina D, Abate V, Cacace G, et al. Tumor-induced Osteomalacia: A Systematic Review and Individual Patient's Data Analysis. *J Clin Endocrinol Metab*. 2022;107(8):e3428-e3436. doi:10.1210/clinem/dgac253
3. Portales-Castillo I, Rieg T, Khalid SB, Nigwekar SU, Neyra JA. Physiopathology of Phosphate Disorders. *Advances in Kidney Disease and Health*. 2023;30(2):177-188. doi:10.1053/J.AKDH.2022.12.011
4. Yin Z, Du J, Yu F, Xia W. Tumor-induced osteomalacia. *Osteoporos Sarcopenia*. 2018;4(4):119-127. doi:10.1016/J.AFOS.2018.12.001
5. Kim KJ, Song JE, Kim JH, et al. Elevated morbidity and mortality in patients with chronic idiopathic hypophosphatemia: a nationwide cohort study. *Front Endocrinol (Lausanne)*. 2023;14. doi:10.3389/fendo.2023.1229750
6. Aligail K, Dave JA, Ross IL. Tumor-induced osteomalacia: a case report. *J Med Case Rep*. 2022;16(1). doi:10.1186/s13256-021-03220-7
7. Jadhav SS, Shah R, Patil V. Tumor-induced osteomalacia: An overview. *Best Pract Res Clin Endocrinol Metab*. 2024;38(2):101834. doi:10.1016/J.BEEM.2023.101834
8. Bosman A, Palermo A, Vanderhulst J, et al. Tumor-Induced Osteomalacia: A Systematic Clinical Review of 895 Cases. *Calcif Tissue Int*. 2022;111(4):367-379. doi:10.1007/s00223-022-01005-8

9. Cundy T, Que L, Hassan IM, Hughes L. Bisphosphonate-Induced Deterioration of Osteomalacia in Undiagnosed Adult Fanconi Syndrome. *JBMR Plus*. 2020;4(8). doi:10.1002/jbm4.10374
10. Lee GJ, Marks J. Intestinal phosphate transport: a therapeutic target in chronic kidney disease and beyond? *Pediatric Nephrology*. 2015;30(3):363-371. doi:10.1007/s00467-014-2759-x
11. Sabbagh Y, Giral H, Caldas Y, Levi M, Schiavi SC. Intestinal Phosphate Transport. *Adv Chronic Kidney Dis*. 2011;18(2):85-90. doi:10.1053/j.ackd.2010.11.004
12. Yee J, Rosenbaum D, Jacobs JW, Sprague SM. Small Intestinal Phosphate Absorption: Novel Therapeutic Implications. *Am J Nephrol*. 2021;52(7):522-530. doi:10.1159/000518110
13. Fukumoto S. The role of bone in phosphate metabolism. *Mol Cell Endocrinol*. 2009;310(1-2):63-70. doi:10.1016/j.mce.2008.08.031
14. Thomas L, Dominguez Rieg JA, Rieg T. Npt2a as a target for treating hyperphosphatemia. *Biochem Soc Trans*. 2022;50(1):439-446. doi:10.1042/BST20211005
15. Bergwitz C, Jüppner H. Regulation of Phosphate Homeostasis by PTH, Vitamin D, and FGF23. *Annu Rev Med*. 2010;61(1):91-104. doi:10.1146/annurev.med.051308.111339
16. Kolek OI, Hines ER, Jones MD, et al. 1α,25-Dihydroxyvitamin D $_3$ upregulates FGF23 gene expression in bone: the final link in a renal-gastrointestinal-skeletal axis that controls phosphate transport. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2005;289(6):G1036-G1042. doi:10.1152/ajpgi.00243.2005
17. Goltzman D, Mannstadt M, Marcocci C. Physiology of the Calcium-Parathyroid Hormone-Vitamin D Axis. In: ; 2018:1-13. doi:10.1159/000486060
18. Aljuraibah F, Bacchetta J, Brandi ML, et al. An Expert Perspective on Phosphate Dysregulation With a Focus on Chronic Hypophosphatemia. *Journal of Bone and Mineral Research*. 2022;37(1):12-20. doi:10.1002/jbmr.4486
19. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 Is a Potent Regulator of Vitamin D Metabolism and Phosphate Homeostasis. *Journal of Bone and Mineral Research*. 2004;19(3):429-435. doi:10.1359/JBMR.0301264
20. Saponaro F, Saba A, Zucchi R. An Update on Vitamin D Metabolism. *Int J Mol Sci*. 2020;21(18):6573. doi:10.3390/ijms21186573
21. Jan de Beur SM, Minisola S, Xia W bo, et al. Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia. *J Intern Med*. 2023;293(3):309-328. doi:10.1111/joim.13593

22. Hori M, Shimizu Y, Fukumoto S. Minireview: Fibroblast Growth Factor 23 in Phosphate Homeostasis and Bone Metabolism. *Endocrinology*. 2011;152(1):4-10. doi:10.1210/en.2010-0800
23. Fukumoto S, Hasegawa Y. Special Issue: "X-Linked Hypophosphatemia." *Endocrines*. 2023;4(4):720-721. doi:10.3390/endocrines4040052
24. Gupta A, Dwivedi A, Patel P, Gupta S. Hypophosphatemic osteomalacia in von Recklinghausen neurofibromatosis: Case report and literature review. *Indian Journal of Radiology and Imaging*. 2015;25(1):63-66. doi:10.4103/0971-3026.150155
25. Obo T, Koriyama N, Tokito A, Ogiso K, Nishio Y. Neurofibromatosis type 1 associated with hypophosphatemic osteomalacia due to hypersecretion of fibroblast growth factor 23: A case report. *J Med Case Rep*. 2020;14(1). doi:10.1186/s13256-020-02381-1
26. Kancherla K, Constantin H, Kanawati A, Graham E. Iron-induced Hypophosphatemic Osteomalacia-An Atypical Case of Bilateral Femoral Stress Fractures. *J Am Acad Orthop Surg Glob Res Rev*. 2023;7(5). doi:10.5435/JAAOSGlobal-D-22-00155
27. Samões B, Silva B, Martins A, et al. Hypophosphatemic osteomalacia induced by intravenous iron therapy: a case report. *Joint Bone Spine*. 2023;90(5):105586. doi:10.1016/J.JBSPIN.2023.105586
28. Vilaca T, Velmurugan N, Smith C, Abrahamsen B, Eastell R. Osteomalacia as a Complication of Intravenous Iron Infusion: A Systematic Review of Case Reports. *Journal of Bone and Mineral Research*. 2022;37(6):1188-1199. doi:10.1002/jbmr.4558
29. He H, Zhang YJ. Multiple-level spinal fractures due to adefovir-induced Fanconi syndrome and hypophosphatemic osteomalacia: A case report. *Asian J Surg*. 2023;46(4):1712-1713. doi:10.1016/J.ASJSUR.2022.09.140
30. Palermo A, Strollo R, Papalia R, et al. Severe hypophosphatemic osteomalacia secondary to fanconi syndrome due to adefovir: A case report. *Endocrine Practice*. 2014;20(12):e246-e249. doi:10.4158/EP14251.CR
31. Wang M, Cao X, Cao B. Hypophosphatemic vitamin D-resistant osteomalacia: A case report. *Exp Ther Med*. 2013;6(3):791-795. doi:10.3892/etm.2013.1209
32. Hawke K, Croft A, Lazarus S. Tumor-Induced Osteomalacia in a Patient with Crohn's Disease: A Case Report and Approach to Investigating Hypophosphatemia. *Case Rep Gastroenterol*. Published online 2024:81-89. doi:10.1159/000536136

33. Li X, Cheng D, Sun Z, Jiao Q, Wang C, Fan Y. An Unusual Case of Bone Pain, Hypophosphatemia, and a Gastric Mass: A Quiz. *American Journal of Kidney Diseases*. 2024;83(3):A16-A20. doi:10.1053/j.ajkd.2023.09.013
34. Ikegawa K, Hasegawa Y. Presentation and Diagnosis of Pediatric X-Linked Hypophosphatemia. *Endocrines*. 2023;4(1):128-137. doi:10.3390/endocrines4010012
35. Fukumoto S. FGF23-related hypophosphatemic rickets/osteomalacia: diagnosis and new treatment. *J Mol Endocrinol*. 2021;66(2):R57-R65. doi:10.1530/JME-20-0089
36. Jiang Y, Li X, Huo L, et al. Consensus on clinical management of tumor-induced osteomalacia. *Chin Med J (Engl)*. 2021;134(11):1264-1266. doi:10.1097/CM9.0000000000001448
37. Takeuchi Y, Suzuki H, Ogura S, et al. Venous Sampling for Fibroblast Growth Factor-23 Confirms Preoperative Diagnosis of Tumor-Induced Osteomalacia. *J Clin Endocrinol Metab*. 2004;89(8):3979-3982. doi:10.1210/jc.2004-0406
38. Minisola S, Fukumoto S, Xia W, et al. Tumor-induced Osteomalacia: A Comprehensive Review. *Endocr Rev*. 2023;44(2):323-353. doi:10.1210/endrev/bnac026
39. Paramba F, Silas M, Masoodi N, Benjamin S, Palaki JA. Hypophosphatemic Osteomalacia in a Young Adult. *Cureus*. Published online March 4, 2021. doi:10.7759/cureus.13697
40. Brunelli SM, Goldfarb S. Hypophosphatemia: Clinical consequences and management. *Journal of the American Society of Nephrology*. 2007;18(7):1999-2003. doi:10.1681/ASN.2007020143
41. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *Journal of Bone and Mineral Research*. 2011;26(7):1381-1388. doi:10.1002/jbmr.340
42. Spaleniak S, Kade G, Kidziński R, Mazurek A, Lubas A, Niemczyk S. Tumor-induced hypophosphatemic osteomalacia as a rare cause of bone pain. *Pol Arch Intern Med*. 2018;128(3):189-191. doi:10.20452/pamw.4234