Osteoporosis International (2019) 30:519–523
https://doi.org/10.1007/s00198-018-4679-2

CASE REPORT

Severe hypophosphatemia induced by denosumab in a patient with osteomalacia and tenofovir disoproxil fumarate-related acquired Fanconi syndrome

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Received: 20 March 2018 / Accepted: 19 August 2018 / Published online: 31 August 2018

Abstract

Denosumab, a novel agent that inhibits osteoclasts, reduces the risk of fracture in patients with osteoporosis. However, worsening of hypophosphatemia and other symptoms may be induced by denosumab in patients with pre-existing hypophosphatemic osteomalacia. A 58-year-old man with hepatitis B presented with diffuse bone pain and muscle weakness. Denosumab was prescribed by the orthopedist according to documented low bone mass and spine compression fracture. After administering denosumab, the patient's bone pain worsened, and he later developed a right tibia stress fracture. His condition was diagnosed as adult-onset hypophosphatemic osteomalacia complicated by multiple bone fractures, which resulted from Fanconi syndrome with proximal tubulopathy due to tenofovir disoproxil fumarate (TDF) treatment for his hepatitis B. Denosumab use leads to aggressive hypophosphatemic osteomalacia and the complication of stress fractures, because of its effects on bone resorption. Physicians should be aware that in patients with chronic hepatitis B monoinfection who are administered TDF therapy, bone pain or fracture is possible but preventable by timely monitoring of serum phosphate levels. Denosumab should not be used in patients with untreated osteomalacia or vitamin D deficiency, as it may lead not only to hypocalcemia but also to hypophosphatemia in these patients.

Keywords Denosumab · Fanconi syndrome · Hypophosphatemia · Osteomalacia · Tenofovir

Introduction

Denosumab (Prolia) is a fully human monoclonal antibody that acts as an osteoprotegerin mimic against the receptor activator of nuclear factor-κB ligand (RANKL) to interfere with osteoclast formation and survival. Denosumab is an anti-resorptive therapy for osteoporosis that may be efficacious in patients with renal impairment [1]. However, it is unsuitable for secondary osteoporosis or metabolic bone diseases such as osteomalacia and primary hyperparathyroidism, which mimic osteoporosis [2, 3]. Denosumab selectively arrests osteoclasts while maintaining intact osteoblast function, and these effects may decrease serum calcium and phosphate levels [1, 4].

Tenofovir disoproxil fumarate (TDF) is a nucleotide analog reverse transcriptase inhibitor approved by the US Food and Drug Administration as an effective first-line option for treating infection by chronic hepatitis B virus (HBV) or human immunodeficiency virus (HIV) [5, 6]. Previous studies suggest that TDF increases the risk of proximal tubular dysfunction, acute renal failure, chronic renal failure, and nephrogenic diabetes insipidus [7, 8]. Although uncommon, the occurrence of Fanconi syndrome in TDF-treated patients with hepatitis B virus monoinfection was recently reported [9, 10]. Fanconi syndrome is characterized by proximal tubular dysfunction, leading to increased urinary excretions of glucose, protein, bicarbonate, phosphorus, and possible hypophosphatemic osteomalacia. Without adequate vitamin D and phosphate treatments for hypophosphatemic osteomalacia, denosumab may increase the severity of pre-existing hypocalcemia and hypophosphatemia.

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Here, we present a case of hypophosphatemic osteomalacia secondary to TDF-induced Fanconi syndrome misdiagnosed as osteoporosis. Denosumab worsened pre-existing hypophosphatemic osteomalacia through its effects on bone resorption complicated by a right tibia stress fracture.

Case summary

A 58-year-old man with hepatitis B, who had been treated with TDF for 2.5 years, presented with escalating progressive bone pain and muscle weakness. Physical examination results were unremarkable except for proximal muscle weakness. Plain radiography suggested osteoporosis and spinal compression fracture changes (T8–T9, L1–S1; Fig. 1a). The lumbar spine (T-score −2.6) and femoral neck (T-score −3.0) revealed decreased bone mass. The findings of low bone density and spine compression fracture led to a diagnosis of osteoporosis, and denosumab was prescribed by the orthopedist. However, worsening of bone pain, particularly in the right leg, led to wheelchair status and the patient was referred to our clinic. Bone scintigraphy revealed increased tracer uptake over multiple costochondral junctions, creating a rachitic rosary sign and mildly increased intake in the right distal tibia (Fig. 1b). Initial radiological studies revealed no fracture (Fig. 1c), but computed tomography imaging revealed stress fractures of the distal tibia (Fig. 1d, e). The patient's serum creatinine level was 1.15 mg/dL (range 0.7–1.5), his phosphate level was 1.2 mg/dL (2.1–4.7), and his uric acid level was 1.8 mg/dL (2.5–7.2). His alkaline phosphatase level was elevated at 281 IU/L (42–128) and his anion gap metabolic acidosis was normal (HCO_3 14.7 mmol/L). Urinalysis revealed increased fractional excretion of phosphate (65%; normal range 5–18%), decreased tubular maximum reabsorption of phosphate per liter of glomerular filtration rate ($TmPO_4$/GFR, 0.14 mmol/L; normal range > 0.8 mmol/L), and normoglycemic glycosuria and proteinuria (100 mg/dL). Other laboratory test results revealed a low total serum calcium concentration of 8.0 mg/dL (8.4–10.6), elevated serum intact parathyroid hormone concentration of 222 pg/mL (15.6–68.3), and low 25-OH-calciferol levels (17.8 ng/mL; normal range 30–100 ng/mL). His initial workup was negative for malignancy. Immunological examination revealed negativity for antinuclear antibodies. The patient was diagnosed with hypophosphatemia osteomalacia secondary to Fanconi syndrome, with worsening of the clinical presentation after treatment with denosumab. TDF therapy was discontinued and entecavir was prescribed. Alkalization with potassium citrate, neutral phosphate, and vitamin D3 and activated vitamin D (calcitriol) supplementation were also prescribed. The patient recovered uneventfully, with relieved diffuse bone pain, right tibia stress fractures (Fig. 1f), and weakness.

Discussion

Patients with Fanconi syndrome are characterized by proximal tubule resorption impairment, causing hypophosphatemia, proteinuria, normoglycemic glycosuria, hypouricemia, and type II renal tubule acidosis. This patient's laboratory abnormalities (increased alkaline phosphatase levels, low 25-OH-calciferol levels, hypocalcemia with secondary hyperparathyroidism, and hypophosphatemia) and rachitic rosary signs suggested osteomalacia. Thus, he was diagnosed with hypophosphatemic osteomalacia secondary to Fanconi syndrome induced by TDF. Other causes worsening the pre-existing hypophosphatemia included vitamin D deficiency with secondary hyperparathyroidism and denosumab administration. A limitation of this case report is that the patient's phosphate level was not evaluated before denosumab administration. The effects of denosumab in selectively inhibiting osteoclast function with minimal changes in osteoblastic function may increase bone mass and induce hypocalcemia and hypophosphatemia. The patient's hypophosphatemia worsened, as his symptoms progressed just after denosumab administration. Another differential diagnosis of urinary phosphate wasting is tumor-induced osteomalacia, which is related to increased serum fibroblast growth factor 23 (FGF-23) levels, a molecule secreted by rare mesenchymal tumors [11]. Unfortunately, no method is available for confirming serum FGF-23 levels in our hospital. Nevertheless, tumor-induced osteomalacia is characterized by isolated urinary phosphate wasting and this diagnosis was unlikely, as the patient presented with Fanconi syndrome. Furthermore, the patient finally recovered without tumor resection.

Both osteomalacia and osteoporosis affect bone structure, but through different mechanisms. Osteoporosis reduces bone density, while osteomalacia impairs mineralization. Osteomalacia and osteoporosis also present distinguishable clinical manifestations. For example, muscle weakness and bone pain are more common in osteomalacia than in osteoporosis, particularly without bone fractures. Bone densitometry is one modality used to detect low bone mass, but osteoporosis and osteomalacia cannot be differentiated using this method, as bone turnover and mineralization cannot be differentiated [2, 3]. Previous studies reported bone density reductions due to treatment with TDF [12, 13]. Possible mechanisms for tenofovir-associated bone loss have been suggested, including (1) uptake of TDF by osteoblasts and osteoclasts, which alters gene expression and interferes with the balance of bone resorption and formation, and (2) tenofovir-induced proximal tubule dysfunction and Fanconi syndrome, resulting in renal phosphate wasting and subsequent bone demineralization [12, 13].

Fig. 1 Characteristic radiological and bone scan findings in a patient with osteomalacia. **a** Plain radiological images of several vertebrae, **b** whole-body bone scintigraphy, **c** plain radiography of the distal tibia with a mild periosteal reaction (arrows), **d**, **e** computed tomography images of the insufficient linear fractures of the right distal tibia (arrows), and **f** recovery of whole-body bone scintigraphy with a decrease in radiotracer uptake compared to previous images

The patient was incorrectly diagnosed as having osteoporosis and was administered denosumab. However, this treatment was not suitable for the patient. Fanconi syndrome-related hypophosphatemic osteomalacia is mainly due to renal phosphate wasting complicated by defects in mineralization rather than bone turnover or bone mass. Phosphorus

metabolism is complex, and serum phosphate levels are determined by the balance between intestinal phosphorus absorption, tubular reabsorption, and ion exchange between intracellular and bone pools. In addition to the well-known parathyroid hormone-calcitriol axis, other components participate actively in this regulation. Renal proximal tubular reabsorption of phosphorus is a critical variable in systemic phosphorus homeostasis, in which 85% of filtered inorganic phosphorus is reabsorbed, leaving a small amount for reabsorption in Henle's loop and distal tubules [14]. The patient may have developed hypophosphatemia because of Fanconi syndrome. Furthermore, denosumab selectively inhibits osteoclasts without inhibiting osteoblast function, which can induce hypocalcemia and hypophosphatemia. Without an adequate phosphate and vitamin D supply, the effects of denosumab may have worsened pre-existing hypophosphatemic osteomalacia to more symptomatic hypophosphatemia, which was complicated by more severe mineralization impairment and decreased bone quality to induce a right tibia stress fracture.

A stress fracture is a repetitive strain injury caused by a mechanical load that is not sufficient to cause a fracture. Stress fractures are associated with various diseases such as osteoporosis and multiple myeloma, as well as metabolic bone diseases such as hyperparathyroidism and osteomalacia [15]. Because stress fractures tend to be incomplete and therefore undisplaced, their identification on radiographs can be challenging. Other imaging modalities such as scintigraphy and computed tomography are useful. Scintigraphy findings are often positive within days after a fracture, but it may take weeks before an abnormality appears on a scintigram. In computed tomography, stress fractures appear as linear areas of sclerosis with or without associated linear lucency through the adjacent cortex [16]. Clinical acumen is necessary to determine a diagnosis by collating clinical assessments with radiographic findings.

In conclusion, physicians should be aware that in patients with chronic hepatitis B monoinfection receiving TDF therapy, bone pain or fracture is possible. Early diagnosis of hypophosphatemic osteomalacia secondary to Fanconi syndrome and the immediate discontinuation of TDF are essential for reducing complications associated with TDF treatment. More importantly, close monitoring of blood phosphate as a marker of tubular disease, as well as the role of urine beta 2-microglobulin-to-creatinine ratio and $TmPO_4$/GFR, is needed for a more specific diagnosis of tenofovir-induced Fanconi syndrome [5]. Tenofovir alafenamide (TAF) is a new formula of tenofovir that has been approved for the treatment of HIV and HBV with lower nephrotoxicity. TAF should be the preferred formulation of tenofovir to minimize nephrotoxicity [17, 18]. Denosumab is unsuitable for treating hypophosphatemic osteomalacia, as it may lead to hypocalcemia [18, 19] and hypophosphatemia in patients in which phosphate homeostasis is dependent on high bone turnover. Additionally, clinical physicians should exclude diagnoses of other metabolic bone diseases, such as osteomalacia, before administering denosumab. Imaging modalities such as scintigraphy and computed tomography may be useful in detecting stress fractures in these patients.

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Compliance with ethical standards

Informed consent Informed consent was obtained from the participant included in this study.

Conflicts of interest None.

References

1. Block GA, Bone HG, Fang L, Lee E, Padhi D (2012) A single-dose study of denosumab in patients with various degrees of renal impairment. J Bone Miner Res 27(7):1471–1479
2. Taxel P, Kenny A (2000) Differential diagnosis and secondary causes of osteoporosis. Clin Cornerstone 2(6):11–21
3. Babayev R, Nickolas TL (2015) Bone disorders in chronic kidney disease: an update in diagnosis and management. Semin Dial 28(6): 645–653
4. Chen CL, Chen NC, Hsu CY, Chou KJ, Lee PT, Fang HC, Renn JH (2014) An open-label, prospective pilot clinical study of denosumab for severe hyperparathyroidism in patients with low bone mass undergoing dialysis. J Clin Endocrinol Metab 99(7): 2426–2432
5. European Association For The Study Of The Liver (2012) EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 57(1):167–185
6. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338(13):853–860
7. Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, Atta MG, Wools-Kaloustian KK, Pham PA, Bruggeman LA, Lennox JL, Ray PE, Kalayjian RC, HIV Medicine Association of the Infectious Diseases Society of America (2014) Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 59(9):e96–e138
8. Tourret J, Deray G, Isnard-Bagnis C (2013) Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? J Am Soc Nephrol 24(10):1519–1527
9. Gracey DM, Snelling P, McKenzie P, Strasser SI (2013) Tenofovir-associated Fanconi syndrome in patients with chronic hepatitis B monoinfection. Antivir Ther 18(7):945–948
10. Suh YS, Chun DI, Choi SW, Lee HW, Nho JH, Kwon SH, Cho JH, Won SH (2017) Pathologic femoral fracture due to tenofovir-induced Fanconi syndrome in patient with chronic hepatitis B: a case report. Medicine (Baltimore) 96(46):e8760

11. Boland JM, Tebben PJ, Folpe AL (2018) Phosphaturic mesenchymal tumors: what an endocrinologist should know. J Endocrinol Investig. https://doi.org/10.1007/s40618-018-0849-5
12. Grant PM, Cotter AG (2016) Tenofovir and bone health. Curr Opin HIV AIDS 11(3):326–332
13. Grigsby IF, Pham L, Mansky LM, Gopalakrishnan R, Mansky KC (2010) Tenofovir-associated bone density loss. Ther Clin Risk Manag 6:41–47
14. Villa-Bellosta R, Ravera S, Sorribas V, Stange G, Levi M, Murer H, Biber J, Forster IC (2009) The Na+-Pi cotransporter PiT-2 (SLC20A2) is expressed in the apical membrane of rat renal proximal tubules and regulated by dietary Pi. Am J Physiol Renal Physiol 296(4):F691–F699
15. McKenna MJ, Heffernan E, Hurson C, McKiernan FE (2014) Clinician approach to diagnosis of stress fractures including bisphosphonate-associated fractures. QJM 107(2):99–105
16. Krestan CR, Nemec U, Nemec S (2011) Imaging of insufficiency fractures. Semin Musculoskelet Radiol 15(3):198–207
17. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH (2016) American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 63(1):261–283
18. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, Pozniak A, Thompson M, Podzamczer D, Molina JM, Oka S, Koenig E, Trottier B, Andrade-Villanueva J, Crofoot G, Custodio JM, Plummer A, Zhong L, Cao H, Martin H, Callebaut C, Cheng AK, Fordyce MW, McCallister S, Team G-U-S (2015) Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 385(9987):2606–2615
19. Shafqat H, Alquadan KF, Olszewski AJ (2014) Severe hypocalcemia after denosumab in a patient with acquired Fanconi syndrome. Osteoporos Int 25(3):1187–1190