Case Report   **EP171982.CR**

LIFE-THREATENING HYPOCALCEMIA IN A PATIENT WITH HIGHLY SUSPECTED OSTEOMALACIA: A

CASE REPORT

Marco Infante MD[1,2], Diana Corradini MD[1,2], Maria Romano MD[2], Alfonso Bellia MD, PhD[1,2], Davide Lauro MD[1,2]

From[. 1] Department of Systems Medicine, University "Tor Vergata", Rome, Italy
[2] Endocrinology Unit, Department of Medicine, University Hospital Policlinico Tor Vergata, Rome, Italy

Running Title: Severe hypocalcemia in osteomalacia

Corresponding address: Prof. Davide Lauro, MD
University of Rome "Tor Vergata"
Department of Systems Medicine
Via Montpellier 1
I-00133 Rome, Italy
E-mail: d.lauro@med.uniroma2.it

Keywords: Hypocalcemia, Osteomalacia, Vitamin D deficiency, Elderly

Word count: 1789

Number of figures and tables: 4

Abstract

Objective: Osteomalacia is a metabolic bone disease characterized by impaired mineralization with increased non-mineralized osteoid tissue, increased frailty and reduced bone mineral density. A common cause of osteomalacia in adults/elderly is severe deficiency of vitamin D, which leads to chronic hypocalcemia, hypophosphatemia and secondary hyperparathyroidism. Objective of this case report is to describe an unusual clinical presentation of osteomalacia, consisting in life-threatening acute hypocalcemia.

Methods: Clinical, laboratory and imaging data are presented.

Results: We report the case of a 65-year-old man that showed symptoms and signs of severe and prolonged hypocalcemia due to unrecognized vitamin D deficiency. He presented at the Emergency Room reporting abdominal pain and vomiting since the evening before. Blood tests showed increase of rhabdomyolysis markers, severe hypocalcemia, hypophosphatemia, hypomagnesemia, normal renal function, elevated levels of alkaline phosphatase, along with extremely high levels of PTH and hypovitaminosis D. Radiological skeletal features of bone demineralization and bone abnormalities suggestive of osteomalacia were additionally detected. Other secondary causes of hypocalcemia were excluded. Clinical and biochemical resolution were progressively obtained only after intramuscular loading dose of cholecalciferol was added to standard calcium intravenous replacement therapy.

Conclusion: This case report shows that osteomalacia consequent to a severe vitamin D deficiency can draw attention with acute onset of symptoms and signs of severe hypocalcemia requiring hospital admission. In such cases, vitamin D administration, and not intensive calcium supplementation alone, is essential to achieve clinical resolution of symptoms and normalization of mineral metabolism parameters.

Introduction

Osteomalacia is a metabolic bone disease characterized by impaired mineralization of newly formed organic matrix, potentially deriving from a number of conditions, including vitamin D deficiency, malnutrition, intestinal malabsorption (i.e. celiac disease), chronic liver and kidney disease, renal tubular disorders, phosphate depletion, acidosis, use of certain drugs and neoplasms [1-4]. Severe vitamin D deficiency (defined as 25-OH-D < 10 ng/ml) is definitely the leading cause of osteomalacia in elderly, with symptomatic patients experiencing various disabling complaints, including bone pain responsible for waddling or antalgic gait, muscular weakness and cramps, bone fractures, and progressive fractures-induced skeletal deformities in the most severe cases [5,6]. Typical biochemical findings of osteomalacia consist of: (a) low levels of 25-OH-D, (b) normal/low serum calcium, (c) low phosphate, (d) high levels of PTH, (e) high levels of ALP and osteocalcin [5]. Nevertheless, diagnosis needs to be confirmed by specific radiological features that, although inconstantly, consist of symmetrical radiolucent bands, also known as *pseudofractures* or *Looser's zones*, usually oriented perpendicularly to bone surface [7]. Of note, acute hypocalcemia is not typically reported as clinical feature of osteomalacia. Here we report the case of an elderly patient with unrecognized osteomalacia who developed clinical manifestations of severe treatment-resistant hypocalcemia, and briefly discuss our diagnostic approach and clinical management. Table 1 shows non-standard abbreviations, while Table 2 lists normal ranges for selected blood and urinary parameters used in our Institution.

Case report

A 65-year-old man came to the Emergency Room of Policlinico Tor Vergata University Hospital, Rome (Italy), for abdominal pain and vomiting arisen from the evening before, associated with constipation going on from around a week. Of note, physical examination revealed the presence of persistent paresthesias and difficulty moving arms, especially the hands. Trousseau sign was bilaterally positive, with flexed wrist and metacarpophalangeal joints, extended interphalangeal joints and adducted thumbs after the cuff was inflated. No ongoing medications were reported. Blood tests showed severe hypocalcemia (albumin adjusted-serum calcium 4.9 mg/dl) and hypophosphatemia (inorganic phosphate 1.8 mg/dl), normal renal and liver function, elevated serum ALP (453 IU/l) and increase of rhabdomyolysis biomarkers (CPK 5267 IU/l; myoglobin 7027 ng/ml). Electrocardiogram at admission showed slightly prolonged QT interval (440 msec). CT scan was negative for abdominal acute events. In light of these findings, intravenous saline was promptly initiated to reduce risk of diffuse rhabdomyolysis and acute renal impairment, along with 10% calcium gluconate infusion (4 g of elemental calcium within the first 36 hours), leading to partial recovery of symptoms, ECG signs and rhabdomyolysis markers, but without any significant improvement of albumin adjusted-calcium and inorganic phosphate. Additionally, extremely high intact-PTH (649 pg/ml) was detected. On admission at our Endocrinology Unit, the patient reported a history of frailty, social deprivation, past alcohol abuse and recent surgery for prosthetic left knee due to a road accident, which prevented him from ambulating again. Despite continuous intensive iv administration of 10% calcium gluconate (up to 9 g/daily), albumin adjusted-calcium levels were persistently low (6.1 mg/dl after three days of treatment) with urinary calcium excretion toward the lower limit of normal range (70.2 mg/24h) and normalization of serum inorganic phosphate (3.5 mg/dl). Low magnesium levels were also detected (1.4 mg/dl), along with evidence of caloric malnutrition (prealbumin 10 mg/dl; retinol binding protein 1 mg/dl; transferrin 133 mg/dl; blood lymphocytes 1550/μl, 17.9% of total white blood cells). Mineral metabolism assessment confirmed the high levels of PTH (649 pg/ml), alongside severely impaired vitamin D status (25-OH-D 6.3 ng/ml) and increased biomarkers of bone neo-formation (osteocalcin 104 ng/ml; bone alkaline phosphatase 105 μg/l). During the following days, calcium levels did not substantially increase, despite further intensification of calcium iv supplementation and introduction of oral calcitriol (up to 1 μg/daily) and iv sulphate magnesium (1 g/daily, corresponding to 20 mEq of elemental

magnesium/daily). Meanwhile, potential causes of severe hypocalcemia were investigated. The so-called "hungry bone syndrome", which is frequently associated with acute hypocalcemia, was first excluded since neither thyroidectomy nor parathyroidectomy were reported in the medical history [8]. Autoimmune screening for celiac disease was also negative. Whole-body bone scintigraphy with 99mTc-HMDP excluded osteoblastic bone metastases, whilst showing focal hyperfixation of the osteotropic tracer at the level of ribs and distal third of the left tibia (Figure 1), both attributable to post-traumatic lesions and previous fractures, as reported by the patient himself. Upper abdomen ultrasound and high resolution chest CT scan, along with the abdominal CT scan previously performed in Emergency Room, excluded solid neoplasms. DXA analysis revealed remarkable reduction of BMD at both L2-L4 lumbar spine (BMD 0.671 g/cm^2, T-score -3.8 SD) and non-dominant proximal femur (BMD 0.348 g/cm^2, T-score -4.5 SD), consistently with the recent history of fractures and the evidence of hyperparathyroidism. Skeletal survey showed widespread joint degenerations at level of the cervical spine with reduction of interbody spaces, marked accentuation of the dorsal kyphosis, decreased bone mineralization, remarkable diminution of long bones opacity in the arms and a varus attitude of the first foot ray bilaterally. These radiological skeletal features were highly suggestive of osteomalacia, although not fully diagnostic as the characteristic *pseudo-fractures* of osteomalacia were not described [7]. Bone biopsy confirmation was unfortunately not available because of patient refusal [9]. Persistence of severe hypocalcemia despite extremely high serum levels of PTH raised the question of peripheral resistance to PTH with subsequent development of functional autonomy by parathyroid glands. To address this issue, neck ultrasonography followed by parathyroid scintigraphy with 99mTc sestamibi were performed, excluding the presence of hyperfunctional autonomous parathyroid tissue. Diagnosis of pseudohypoparathyroidism was also excluded given the lack of typical somatic features of Albright hereditary osteodystrophy, lack of hyperphosphatemia and impaired response of pituitary-thyroid, -gonadal and -growth hormone axes, which are common expression of the multiple hormone-resistance observed in that syndrome [10]. Cranial CT scan was also performed to exclude calcifications of the basal ganglia, a common finding in patients with Fahr's syndrome, a rare degenerative and neuropsychiatric syndrome frequently associated with unexplained hypocalcemia and typically characterized by bilateral deposits of calcium in the basal ganglia and the cerebral

cortex [11]. Genetics counseling excluded other potential differential diagnoses, such as Gitelman syndrome and the above-mentioned pseudohypoparathyroidism. Since no alternative causes for severe hypocalcemia other than deficient vitamin D status were detected, mineral replacements therapies were integrated by cholecalciferol supplementation (loading dose of 300.000 IU im) [12], accompanied by progressive improvement of both calcium and PTH levels (Table 3). Calcium iv infusion was therefore replaced by oral calcium carbonate (3 g/daily) within seven days from cholecalciferol administration. A further ECG documented normalization of QT interval (362 msec). The patient was finally discharged with prescription of oral calcium carbonate (tapered to 1.5 g/daily, according to calcium levels), accompanied by oral calcifediol (75 µg/daily) to be initiated after one month from discharge. Table 3 reports progressive improvements in mineral metabolism parameters, including normalization of PTH and 25-OH-D levels up to 60 days from initial vitamin D replacement.

Discussion

Severe vitamin D deficiency is recognized as the most frequent cause of osteomalacia worldwide [13], leading to hypocalcemia, hypophosphatemia and secondary hyperparathyroidism, which chronically develop over time. Noteworthy, our patient showed vitamin D deficiency with related skeletal abnormalities suggestive of osteomalacia. In such case, the pathogenesis of vitamin D deficiency is likely to be multifactorial. As a matter of fact, the patient was a housebound elderly man, so that lack of sun exposure resulting in decreased capacity for cutaneous production of cholecalciferol (typically observed with advancing age) could have primarily contributed to the vitamin D deficiency [14-16]. In addition, blood examinations were consistent with established caloric malnutrition, so that a concomitant low dietary intake of vitamin D and calcium was highly suspected. Finally, past alcohol abuse reported in the clinical history could have additionally affected the poor calcium/vitamin D status and impaired bone health, as confirmed by spinal and femoral DXA analysis [17]. Having this said, even though a component of malabsorption could not fully ruled out in this patient, nutritional deficiency is likely to have played a major role in determining the disease. as a confirmation, the final control of 25-OH-D, namely after one month of oral supplementation with calcifediol, was substantially higher than baseline levels and above the diagnostic threshold for deficiency.

The man presented to Emergency Room because of acute abdominal pain and vomiting, associated with features of rhabdomyolysis. Although adequate iv calcium supplementation was promptly initiated, substantial recovery of hypocalcemia was achieved only after cholecalciferol administration, supporting that calcium supplementation alone could not be fully effective in such cases. The management of this clinical case suggests some additional considerations. First, vitamin D deficiency should be suspected and routinely investigated in elderly patients presenting with otherwise unexplainable hypocalcemia. Second, vitamin D deficiency, especially when sustained for a long period of time, can lead to a markedly impaired bone mineralization, resulting in a sort of "hungry bone syndrome" which is unlikely to be resolved with calcium supplementation only [18]. Although osteomalacia with symptomatic hypocalcemia is considered a rare finding even with vitamin D levels below 10 ng/ml, this is what probably happened in our elderly patient, for a number of reasons collectively resulting in a nutritional deficiency. As a matter of fact, initial recovery of serum calcium was achieved only after im cholecalciferol was administered, alongside high doses of iv calcium, suggesting for vitamin D replacement to play a central role in restoring adequate bone mineralization process and eventually normocalcemia. Third, there is no general consensus on the type of pharmaceutical formulation of vitamin D, as well as on route of administration, loading and maintenance dose to recommend in such cases. In this sense, the management and empirical treatment approach we described in this patient could be of help in other cases of treatment-resistant acute hypocalcemia. Apart from clinical management of the acute disease, early detection of vitamin D deficiency with its related complications plays a crucial role in a sizeable part of population. This concept is reinforced by the fact that chronic mild to moderate hypocalcemia may be suddenly worsened by various unexpected occurrences (i.e. concomitant use of certain drugs), superimposed to chronic vitamin D deficiency. Accordingly, clinical practice guidelines released by Endocrine Society [19] recommend screening for high-risk individuals, including patients with osteoporosis or malabsorption syndrome, as well as obese (BMI > 30) and generally defined "frail" individuals. In conclusion, this case-report suggests that severe and prolonged vitamin D deficiency may result in acute hypocalcemia syndrome requiring hospitalization. Screening programs directed to early diagnosis of

hypovitaminosis D, especially in frail elderly people, can help to prevent these life-threatening complications, as well as bone chronic injuries related to osteomalacia.

Conclusion

This case report showed that severe vitamin D deficiency in elderly and frail individuals, which is frequently asymptomatic, can additionally lead to marked skeletal mineralization abnormalities affecting routine daily activities, along with life-threatening hypocalcemia requiring hospitalization.

Disclosure Statement: The authors have no multiplicity of interest to disclose.

Ethical Approval: We state that all procedures performed in this study were in accordance with the ethical standards of the research committee of our Institution and with the 1964 Helsinki declaration and its later amendments.

Informed Consent: A written informed consent was obtained by the patient mentioned in this manuscript.

References:

1. **Bhan A, Rao AD, Rao DS**. Osteomalacia as a result of vitamin D deficiency. *Endocrinol Metab Clin North Am*. 2010;39:321-331.

2. **Lawson J.** Drug-induced metabolic bone disorders. *Semin Musculoskelet Radiol*. 2002;6:285-297.

3. **Dadoniene J, Miglinas M, Miltiniene D, et al.** Tumour-induced osteomalacia: a literature review and a case report. *World J Surg Oncol*. 2016;14:4.

4. **Rader CP, Corsten N, Rolf O**. Osteomalacia and vitamin D deficiency. *Orthopade*. 2015;44:695-702.

5. **Reuss-Borst MA.** Metabolic bone disease osteomalacia. *Z Rheumatol*. 2014;73:316-322.

6. **Reginato AJ, Coquia JA**. Musculoskeletal manifestations of osteomalacia and rickets. *Best Pract Res Clin Rheumatol*. 2003;17:1063-1080.

7. **Nowell S, Evans PR, Kurrein F.** Multiple Spontaneous "Pseudo-fractures" of Bone (Milkman's Syndrome). *Br Med J*. 1951;2:91–94.

8. **Brasier AR, Nussbaum SR**. Hungry bone syndrome: clinical and biochemical predictors of its occurrence after parathyroid surgery. *Am J Med*. 1988;84:654-660.

9. **Francis RM, Selby PL.** Osteomalacia. *Baillieres Clin Endocrinol Metab*. 1997;11:145-163.

10. **Mantovani G, Spada A, Elli FM**. Pseudohypoparathyroidism and Gsα-cAMP-linked disorders: current view and open issues. *Nat Rev Endocrinol*. 2016;12:347-356.

11. **Soares FB, Amorim FF, Santana AR, et al.** Fahr's Syndrome due to Hypoparathyroidism Following Thyroidectomy. *Journal of Medical Cases*. 2013;4:380-384.

12. **Diamond TH, Ho KW, Rohl PG, Meerkin M.** Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data. *Med J Aust*. 2005;183:10-12.

13. **Okazaki R.** Vitamin D insufficiency/deficiency: its clinical significance and treatment. *Clin Calcium* 2016;26:251-258.

14. **MacLaughlin J, Holick MF.** Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest*. 1985;76:1536-1538.

15. **Bosomworth NJ.** Mitigating epidemic vitamin D deficiency: the agony of evidence. *Can Fam Physician*. 2011;57:16-20.

16. **Caprio M, Infante M, Calanchini M, et al.** Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects. *Eat Weight Disord*. 2017;22:27-41.

17. **Santolaria F, González-Reimers E, Pérez-Manzano JL, et al.** Osteopenia assessed by body composition analysis is related to malnutrition in alcoholic patients. *Alcohol*. 2000;22:147-157.

18. **Chehaiber MM, Jensen JE**. Hungry bone syndrome due to vitamin-D deficiency. *Ugeskr Laeger*. 2009;171:2925-2926.

19. **Holick MF, Binkley NC, Bischoff-Ferrari HA, et al.** Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911-30.
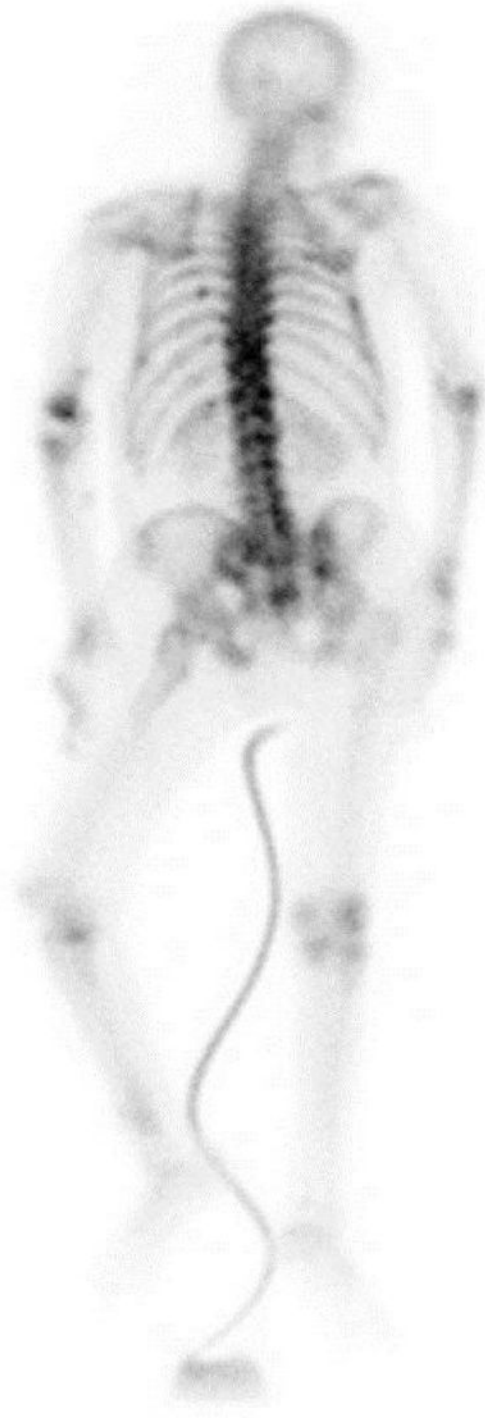
Figure legends:

Figure 1 - Whole-body bone scintigraphy with 99mTc-HMDP 740 MBq: a) anterior view b) posterior view. 99mTc-HMDP: 99mTc-Hydroxymethylene diphosphonate; MBq: megabecquerel.

a   b

Table 1 – List of non-standard abbreviations	
25-OH-D	25-hydroxyvitamin D
99mTc-HMDP	99mTc-Hydroxymethylene diphosphonate
ALP	Alkaline phosphatase
BMD	Bone mineral density
BMI	Body mass index
CPK	Creatine phosphokinase
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
im	Intramuscular
iv	Intravenous
PTH	Parathyroid hormone
SD	Standard deviation

Table 2 – Normal ranges for various blood and urinary parameters at our Institution

Parameter	Normal range
24h urinary calcium excretion	42 - 350 mg/24h
ALP	40 - 129 IU/l
Bone alkaline phosphatase	6 - 33 µg/l
Calcium	8.8 - 10.2 mg/dl
CPK	10 - 190 IU/l
Inorganic phosphate	2.7 - 4.5 mg/dl
Intact-PTH	14 - 72 pg/ml
Lymphocytes	20 - 45% of total white blood cells
Magnesium	1.5 - 2.5 mg/dl
Myoglobin	14 - 110 ng/ml
Osteocalcin	10 - 46 ng/ml
Prealbumin	20 - 40 mg/dl
Retinol binding protein	3 - 6 mg/dl
Transferrin	200 - 360 mg/dl

Abbreviations - ALP: Alkaline phosphatase; CPK: Creatine phosphokinase; Intact-PTH: Intact-Parathyroid hormone

Mineral metabolism parameters (normal range)	At admission	7 days after initial vitamin D supplementation	30 days after initial vitamin D supplementation	60 days after initial vitamin D supplementation
Intact-PTH (14 - 72 pg/ml)	649	442	125	50
Albumin adjusted-calcium (8.8 - 10.2 mg/dl)	4.9	8.6	9.1	9.4
Inorganic Phosphate (2.7 - 4.5 mg/dl)	1.8	3.1	4.3	3.8
25-hydroxy vitamin D (deficiency < 20 ng/ml)	6.3	9.4	12.7	23.4

Table 3 – Mineral metabolism parameters of our patient before and after vitamin D replacement therapy (loading dose with cholecalciferol 300.000 IU im followed by maintenance dose with oral calcifediol 75 µg/daily after one month) and calcium supplementation

Abbreviations - Intact-PTH: Intact-Parathyroid hormone