Internal and Emergency Medicine (2019) 14:447–449
https://doi.org/10.1007/s11739-019-02048-w

IM - PHYSICAL EXAMINATION

Hypocalcemia and hypophosphatemia after treatment with zoledronic acid in a patient with AL amyloidosis

Antonella Tufano[1] · Domenico Rendina[2] · Paolo Conca[1] · Beniamino Matani[1] · Giovanni Di Minno[1]

Received: 17 July 2018 / Accepted: 9 February 2019 / Published online: 15 February 2019

Zoledronic acid (Zol) is the most powerful third generation aminobisphosphonate, can be intravenously (IV) administered, and is commonly used in patients with metabolic and neoplastic bone disorders, including multiple myeloma (MM). Zol reduces osteoclastic activity and promotes cellular apoptosis and can induce both hypocalcemia (HypoCa) and hypophosphatemia (HypoP), usually mild and asymptomatic. The risk of symptomatic severe HypoCa and HypoP, requiring specific treatment, is low, and has been described in patients with additional predisposing risk factors, such as low $25OHD_3$, chronic kidney disease (CKD), and/or liver damage [1–3].

A 54-year-old male affected by immunoglobulin light chain (AL) amyloidosis with renal, hepatic, spleen, bone marrow, and cardiac involvement was admitted to our center for weakness and back pain at April 2018. The AL amyloidosis diagnosis was suspected at August 2015 for the presence of proteinuria, splenomegaly, coagulopathy, caused by reduction of fibrinogen (48 mg/dL), factor IX (8%) and X (7%), and free ʎ light chains with Bence Jones ʎ proteinuria. The diagnosis was confirmed by abdominal fat biopsy. On August 2015, a bone-marrow biopsy was not performed for the severe coagulopathy and no lytic bone lesions/collapsed vertebrae were seen on a whole-body-computed tomography. Biochemical parameters at diagnosis are reported in Table 1. The medical history included also type 2 diabetes mellitus, CKD, and chronic ischemic heart disease. From August 2015 to August 2017, the patient had been treated with chemotherapy (dexamethasone, cyclophosphamide, and bortezomib), but the treatment was stopped after five cycles for the occurrence of severe thrombocytopenia. As reported in Table 1, at the treatment discontinuation, no response to therapy was observed according to criteria proposed by Palladini et al. [4] At February 2018, for the worsening of anemia and thrombocytopenia, a bone-marrow biopsy was performed showing large areas of amyloid deposition and excluding the diagnosis of MM. At March 2018, about 2 weeks before the in-hospital admission, the patient had been treated with Zol for the instrumental evidence of multiple vertebral fractures. At the Zol infusion, serum calcium (sCa) and phosphate (sP) were normal (Fig. 1). Other parameters are reported in Table 1. The patient had been taking oral cholecalciferol 25,000 IU every 2 weeks for at least 6 months. At in-hospital admission, sCa, sP, parathyroid hormone (PTH), $25OHD_3$, and urea were 6.6 mg/dL [normal range (n.r.) 8.5–10.5], 1.7 mg/dL (n.r. 2.3–4.7), 174 pg/mL (n.r. 14.5–87.1), 6.9 ng/mL (n.r. 30–100), and 53 mg/dL, respectively. Sodium, magnesium, and potassium were normal. Electrocardiography (ECG) showed a prolonged corrected QT interval (QTc Bazett 0.49 s) and frequent monomorphic ventricular ectopic beats with intermittent episodes of a bigeminus. Trousseau's phenomenon and Chvostek's sign were absent. The patient admitted that he had forgotten to follow the advised cholecalciferol therapy in the previous weeks.

The patient was diagnosed as having Zol-induced HypoCa and HypoP, and was treated with IV calcium gluconate 1900 mg/day, oral calcitriol 1 µg/day, oral cholecalciferol 25,000 IU/twice weekly, and oral calcium-carbonate 1 g/day for 7 days, with progressive improvement of fatigue symptoms and progressive normalization of sCa and sP (Fig. 1). The ECG normalized on day 7. After the ECG normalization, IV calcium gluconate was stopped, whereas the remaining oral therapy was continued. On day 9, PTH levels was 35.3 pg/mL. At discharge, on 14 days, sCa, sP, and $25OHD_3$ were 8.7 mg/dL, 3.5 mg/dL, and 15.7 ng/mL, respectively. Oral administration of calcitriol at doses of 0.5 µg/day, cholecalciferol 25,000 IU twice weekly, and

✉ Antonella Tufano
atufano@unina.it

[1] Regional Reference Centre for Coagulation Disorders, Department of Clinical Medicine and Surgery, "Federico II" University of Naples, Via S. Pansini, 5, 80131 Naples, Italy

[2] Department of Clinical Medicine and Surgery, "Federico II" University of Naples, Via S. Pansini, 5, 80131 Naples, Italy

Table 1 Clinical and biochemical parameters measured at the diagnosis, after chemotherapy, at the zoledronate infusion, at the in-hospital admission, and at the hospital discharge in our AL amyloidosis patient

	Diagnosis	After chemotherapy	Zol infusion	In-hospital admission	Hospital discharge
Date	August, 2015	August, 2017	April, 2018	April, 2018	May, 2018
NT-proBNP (pg/mL)	1032	920	983	1081	1029
cTnT (ng/mL)	0.020	0.019	0.013	0.018	0.021
dFLC (mg/dL)	360	290	260	365	366
AL amyloidosis stage	II	II	II	II	II
eGFR (mL/min/1.73 m^2)	87	86	62	28	57
Proteinuria (g/24 h)	3.8	3.4	3.7	4.0	2.8
ALP (U/L)	207	165	266	336	325
ALT (U/L)	13	14	43	19	9
AST (U/L)	19	21	25	13	18
GT (U/L)	232	128	445	284	194
tBil (mg/dL)	1.20	1.02	0.87	1.17	1.11

AL amyloidosis stage was estimated according to criteria proposed by Kumar et al. (https://doi.org/10.1200/JCO0.2011.38.5724). In particular, AL amyloidosis patients were assigned a score of 1 for each of NT-ProBNP ≥ 1800 pg/mL, cTnT ≥ 0.025 ng/mL, and dFLC ≥ 18 mg/dL, creating stages I–IV with scores of 0–3 points, respectively

NT-proBNP N-terminal pro-B-type natriuretic peptide (normal value < 125 pg/mL), *cTnT* cardiac troponin-T (normal value < 0.04 pg/mL), *dFLC* difference between involved and uninvolved light chains, *Zol* zoledronate, *eGFR* glomerular filtration rate (Cockcroft–Gault equation), *ALP* alkaline phosphatase (normal range 40–147 U/L), *ALT* alanine transaminase (normal range 10–40 U/L), *AST* aspartate transaminase (normal range 7–56 U/L), *γGT* gammaglutamyltranspeptidase (normal range 9–48 U/L), *tBil* total bilirubin (normal range 0.1–1.2 mg/dL)

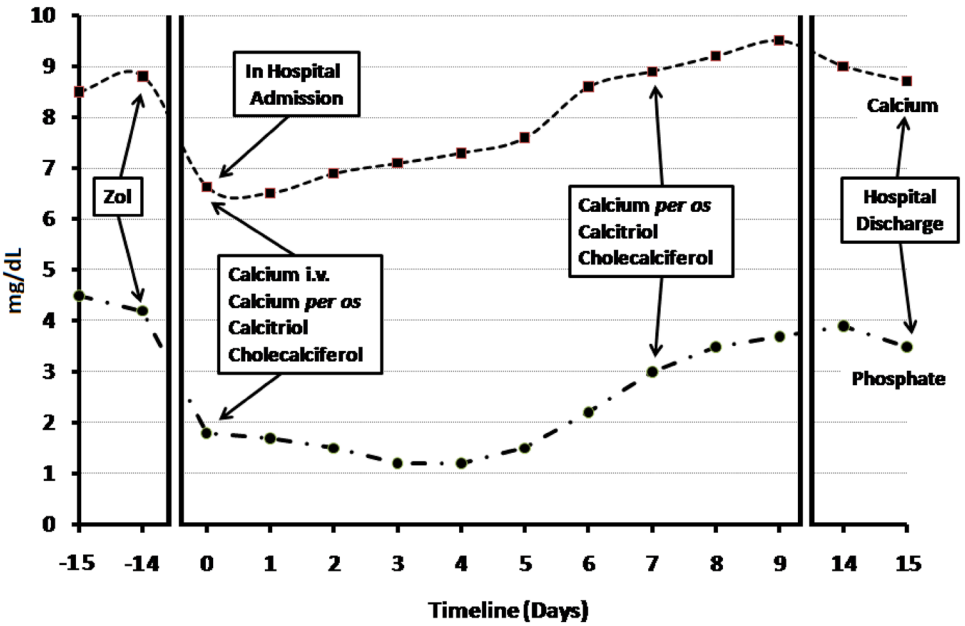

Fig. 1 Overall trend of the serum levels of total calcium (albumin corrected) and phosphate in our patient. *Zol* zoledronic acid 4 mg intravenously administered, *Calcium i.v.* calcium gluconate 1900 mg/day intravenously administered, *Calcium per os* calcium-carbonate 1 g/day orally administered, *Calcitriol* calcitriol 1 g/day orally administered, *Cholecalciferol* cholecalciferol 25,000 IU orally administered/twice weekly

calcium citrate 1000 mg/day was prescribed at discharge. Based on levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin-T (cTnT) and difference between involved and uninvolved light chains (dFLC), the patient was at stage II AL amyloidosis during the entire observation (Table 1).

AL amyloidosis is a monoclonal plasma cell disorder characterized by accumulation of amyloid fibrils in various organs, including heart, kidney, liver, ultimately leading to organ dysfunction/failure. Patients with AL amyloidosis can also have bone disorders, both in the presence and in the absence of MM. In particular, 13 cases of vertebral fractures in AL amyloidosis patients without MM were recently described. In all the cases reported, the vertebral fractures occurred in patients with liver and bone-marrow involvement, as in the present case [5]. The vertebral fractures

in AL amyloidosis may be caused by the deposition of amyloid near vessels supporting vertebrae [5], but, in our patient, additional causes of pathological fractures were: renal/hepatic osteodystrophy and treatment with high-dose dexamethasone. The treatment of vertebral fractures in AL amyloidosis patients is not well established and includes laminectomy, kyphoplastic, palliative radiation, autologous stem cell transplantation, symptomatic-relief drugs, bisphosphonates (three patients), and/or combination of these treatments [5]. No data are available regarding the occurrence of HypoCa and HypoP after Zol treatment in AL amyloidosis patients, although these mineral disorders can occur contextually after infusion [3]. In particular, Zol lowers serum calcium in hypercalcemic, normocalcemic, and hypocalcemic individuals inhibiting osteoclast functions and survival. A compensatory increase in PTH prevents HypoCa by stimulating the renal reabsorption of calcium, the $1,25(OH)_2D_3$ biosynthesis, and the osteoclasts metabolic activities [1–3]. These mechanisms may be impaired in patients with low $25OHD_3$ levels and in those with CKD and/or liver damage. The increased urinary excretion of phosphate, which results from secondary hyperparathyroidism, may also significantly contribute to HypoP after Zol infusion. The quick and complete response to combined treatment with calcium salts, cholecalciferol and calcitriol is an additional suggestion that an impairment of the $25OHD_3/1,25(OH)_2D_3$ system could play a central role in the pathogenesis of HypoCa and HypoP occurred after Zol infusion in our patient. The lack of estimation of the renal tubular reabsorption of phosphate (TmP/GFR) may be considered a limitation in this case, not allowing the evaluation of the mechanisms leading to HypoP. However, TmP/GFR is not a key parameter for management of symptomatic HypoCa with ECG changes, and elevated PTH levels associated to low $25OHD_3$ levels, observed in our patient, are universally considered a possible cause of HypoP after aminobisphosphonate infusion [1–3].

The present report, which for the first time describes the occurrence of both HypoCa and HypoP after Zol infusion in a patient with AL amyloidosis and vertebral fractures, indicates that: (a) sCa and sP should be closely monitored in the days following Zol infusion in patients with CKD and/or liver damage; (b) patients with CKD and/or liver damage could need combined treatment with cholecalciferol and calcitriol, in addition to calcium salt, to correct both HypoCa and HypoP after Zol infusion; and (c) before the infusion, vitamin D status should be evaluated and, as possible, corrected.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Written informed consent was obtained by the patient.

References

1. Kreutle V, Blum C, Meier C, Past M, Müller B, Schütz P, Borm K (2014) Bisphosphonate induced hypocalcaemia—report of six cases and review of the literature. Swiss Med Wkly 144:w13979
2. Clark SL, Nystrom EM (2016) A case of severe, prolonged, refractory hypophosphatemia after zoledronic acid administration. J Pharm Pract 29(2):172–176
3. Kaur U, Chakrabarti SS, Gambhir IS (2016) Zoledronate induced hypocalcemia and hypophosphatemia in osteoporosis: a cause of concern. Curr Drug Saf 11(3):267–269
4. Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, Schönland S, Hegenbart U, Comenzo R, Kastritis E, Dimopoulos MA, Jaccard A, Klersy C, Merlini G (2012) New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol 30(36):4541–4549
5. Wu X, Feng J, Cao X, Zhang L, Zhou D, Li J (2016) A typical immunoglobulin light chain amyloidosis: spontaneous vertebral compression fracture, liver involvement, and bone marrow involvement report of 3 cases and review of the literature. Medicine (Baltimore) 95(36):e4603