Immobilization-Related Hypercalcemia in a COVID-19 Patient With Prolonged Intensive Care Unit Stay

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Abstract: Immobilization-related hypercalcemia is an uncommon finding in patients admitted to intensive care unit. We report a case of severe hypercalcemia in a COVID-19 patient admitted to intensive care unit for hypoxemic respiratory failure. He developed an acute kidney injury requiring continuous renal replacement therapy with regional citrate anticoagulation. Citrate chelates ionized calcium and stop the coagulation cascade locally, preventing filter clotting. Calcium is then given intravenously to a specific target (normocalcemia). It is only when calcium infusion has been stopped that bone resorption and hypercalcemia were unmasked.

Key Words: Immobilization-Induced Hypercalcemia, Continuous Renal Replacement Therapy, Regional Citrate Anticoagulation, COVID-19

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Severe hypercalcemia in intensive care unit (ICU) is an uncommon finding and classically related to hematological malignancy, solid tumors, or endocrinopathies.[1] Immobilization hypercalcemia is rare and classically described in patients with prolonged immobilization like spinal cord injury[2] or burns,[3] which uncouples bone remodeling because of the lack of mechanical stress,[4] and patients with acute or chronic kidney failure are at increased risk of developing severe hypercalcemia when specific conditions are met.[3,5]

Severe acute kidney injury is managed in ICU by using renal replacement therapy. To prevent filter clotting, systemic heparin or regional citrate anticoagulation are the two main anticoagulation strategies used in daily practice. The latter has become the standard of care as prolonged filter life span with lower complications is described.[6] Regional citrate anticoagulation consists of a citrate infusion to the blood before the filter of the extracorporeal circuit, thereby chelating ionized calcium, a key cofactor of many steps of the coagulation cascade. The calcium-citrate complexes are then removed by filtration or metabolized by the liver and muscle. Calcium is then given intravenously with continuous infusion to maintain ionized calcium within normal range.

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This case report conforms to all CAse REports guidelines and reports the required information accordingly (see Supplemental Digital Content 1, http://links.lww.com/PHM/B414).

CLINICAL CASE

A 65-yr-old man was admitted to our hospital for type 1 respiratory failure due to SARS-CoV-2 pneumopathy. His medical history includes insulin-dependent type 2 diabetes and left cerebellum cerebrovascular accident with full recovery.

The day after hospital admission, the patient was transferred to our ICU with severe respiratory failure. Dexamethasone and high flow nasal cannula oxygenation were started. On day 15 of his admission in ICU, the patient was intubated for worsening respiratory failure. Conventional treatment for severe acute respiratory distress syndrome was initiated: prone positioning when $PaO_2/FiO_2 < 150$, transitory neuromuscular blocking agent, and ventilatory associated pneumonia prevention. One month after his admission, continuous veno-venous hemofiltration with regional citrate anticoagulation was started for worsening acute kidney injury (Kidney Disease Improving Global Outcomes as acute kidney injury requiring renal replacement therapy). He was enterally fed during all his ICU stay and never received parenteral nutrition.

He was tracheotomized after 40 days of mechanical ventilation, when oxygen requirements started to improve. The patient was slowly weaned from mechanical ventilation. In the meantime, renal function improved and continuous veno-venous hemofiltration was switched to intermittent hemodialysis (citrate). It was stopped at day 70. On day 90, tracheotomy was removed.

Slowly, after stopping dialysis, the patient developed hypercalcemia, which started to be symptomatic. He started to complain about numbness of the limbs, confusion, and alteration of consciousness. Self-resolving severe bradycardia occurred several times. In the meantime, renal function was deteriorating. Total calcemia culminated at 3.13 mmol/l (corrected calcium = 2.94 mmol/l) and ionized calcium of 1.63 mmol/l (Fig. 1).

Classical workup was realized (Table 1): parathyroid hormone (PTH) was decreased excluding PTH-related hypercalcemia. 25-Hydroxy vitamin D_3 and 1,25-hydroxy vitamin D_3 were low. Workup was completed by excluding onco/hematologic disease. Serum and urine protein electrophoresis, carcinoembryonic antigen (<5 μg/l), prostate specific antigen (<2.5 μg/l), and PTH-related peptide (<20 pg/ml) were normal. Fluorodeoxyglucose positron emission tomography scanner found cutaneous and subcutaneous calcium deposits moderately hypermetabolic and focal hypermetabolic rectal lesion (Supplemental Digital Content 2, http://links.lww.com/PHM/B415). Rectosigmoidoscopy and biopsies excluded potential neoplasia. Thyroid tests were within reference range. A high telopeptide C of 1306 pg/ml confirmed calcium bone loss.
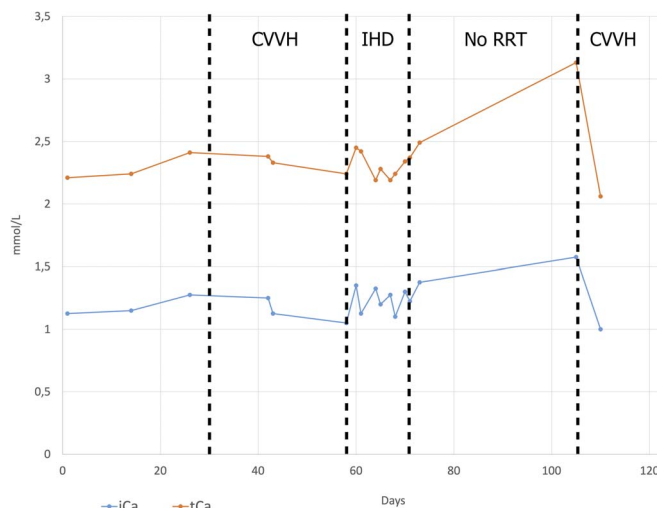
FIGURE 1. Calcium evolution during renal replacement therapy. CVVH, continuous veno-venous hemofiltration; IHD, intermittent hemodialysis.

Pamidronate was given at lower dose (30 mg) in a prolonged infusion due to the potential nephrotoxicity of the drug. One week after the treatment, telopeptide C decreased (21 pg/ml) but hypercalcemia lasted.

The patient developed a *Staphylococcus aureus* septicemia with consciousness alteration and respiratory acidosis. He had to be reintubated and ventilated for 1 day and a half. In the meantime, renal replacement had to be restarted because of worsening renal function. After correcting metabolic disturbance and treating his septicemia with flucloxacilline, the patient was extubated easily but remained with dialysis dependency. As hypercalcemia was refractory to pamidronate, zoledronic acid was given with slower infusion rate (4 mg in 60 mins) 1 mo after with a better control of the calcemia.

Regarding functional condition, the patient was sedated during 3 wks of mechanical ventilation and prone positioning (between 18 and 20 hrs/d). During this period, only passive mobilization and cycle ergometer were possible when patient was supine. When respiratory issues started to improve and that prone position was not required any more (PaO$_2$/FiO$_2$ > 150 mm Hg), sedation was weaned progressively and stopped after tracheotomy. At that time, the patient had severe

critical care neuromyopathy: both in the lower and upper limbs muscle contraction was possible but without associated movement (Medical Research Council scale 1/5). During the weaning process, the patient was mobilized passively to the chair (between 2 and 4 hrs/d) and then progressively actively with the help of the patient. Active periods during cycle-ergometer sessions became more predominant (lower and upper limbs). After 2 mos of hospitalization, the patient was able to stand up with help and walk with a rollator and physiotherapists. Mechanical ventilation was completely weaned after 2.5 mos, and tracheotomy was removed after 3 mos. These events allowed an easier rehabilitation: progression in the walking distances was observed but always with a support of the rollator and help of the physiotherapists.

Patient was then discharged to renal unit, where renal function improved, and dialysis stopped progressively. The patient was then discharged to a long-term facility care with a specific rehabilitation program. Severe disability was still there as classically described in the most severe acute respiratory disease syndrome patient with a prolonged duration of mechanical ventilation and ICU stay (unrelated to the hypercalcemia): the patient was able to walk 10 meters without assistance, with a rollator for 50 meters, and had partially recovered muscle strength (Medical Research Council scale 4/5 on all 4 limbs).

DISCUSSION

Immobilization hypercalcemia is an uncommon diagnosis in ICU despite long stay. Mechanism underlying immobilization related hypercalcemia is not well understood and might be multifactorial. A lack of mechanical stress related to chronic unloading conditions of the muscle and denervation of the sympathetic neural fibers in the bone increases osteoclastic bone resorption. On the other hand, bone formation is reduced by excessive sclerostin production from osteocytes.[2,7]

Usual cause of hypercalcemia needs to be ruled out first by different blood test: PTH, PTH-related peptide, 25-hydroxy vitamin D$_3$, and 1,25-hydroxy vitamin D$_3$. Telopeptide C or N, if elevated, confirm calcium bone loss. Malignancy needs to be excluded as it is the most prevalent cause of hypercalcemia:

TABLE 1. Diagnostic test during the workup of hypercalcemia

Diagnostic Test	Result	Normal
PTH	9 pg/ml	15–80 pg/ml
PTH-related peptide	<20 pg/ml	<20 pg/ml
25-Hydroxy vitamin D$_3$	25 ng/ml	30–100 ng/ml
1,25-Hydroxy vitamin D$_3$	13.7 ng/ml	19.9–79.3 ng/ml
CEA	<5 μg/l	<5 μg/l
PSA	<2.5 μg/l	<2.5 μg/l
TSH	2.17 mU/l	0.27–4.60 mU/l
T4	12 pmol/l	12–22 pmol/l
Telopeptide C (before pamidronate)	1306 pg/ml	100–500 pg/ml
Telopeptide C (after pamidronate)	21 pg/ml	100–500 pg/ml

CEA, carcinoembryonic antigen; PSA, prostate specific antigen; TSH, thyroid stimulating hormone.

fluorodeoxyglucose positron emission tomography scanner is a sensitive examination to exclude this diagnosis.[8]

In our specific case, hypercalcemia was masked by regional citrate anticoagulation renal replacement therapy,[9] which was initiated in a context of acute kidney injury. Hypercalcemia itself can lead to a reversible fall in glomerular filtration rate that is mediated by direct renal vasoconstriction and natriuresis-induced volume contraction. However, in our situation, hypercalcemia was not the cause of acute renal failure as it was not present at baseline and critical COVID-19 is a well-described cause of tubular dysfunction.[10] However, in the second period of the hospitalization, when renal replacement therapy and citrate were stopped, hypercalcemia started to be unmasked and could have played a role in the worsening renal function.

To control hypercalcemia, volume expansion is usually started and medication that could increase calcemia stopped (lithium, thiazide diuretics, vitamin A, theophylline).[11] Calcitonin might be used as a transient treatment while bisphosphonate effect starts. In the specific condition of renal impairment, caution should be given to bisphosphonate.[12] Zoledronic acid has been reported as being superior to pamidronate in reducing hypercalcemia.[13] Reduced doses and slower infusion rate may decrease the risk of nephrotoxicity.

In case of refractory hypercalcemia after this initial treatment, denosumab might be considered. Denosumab acts differently from bisphosphonates as it is a monoclonal antibody with affinity for the receptor activator of nuclear factor-κB ligand. It reduces function and survival of osteoclasts. Potential advantages of denosumab are independent elimination from renal or hepatic function, longer duration, and subcutaneous injection.[14]

The best treatment remains mobilization.[15] Patients developing SARS-CoV-2 respiratory failure were typically ventilated longer than in typical acute respiratory disease syndrome. More than half of patients on prolonged mechanical ventilation have functional limitations after discharge from hospital that may last many years.[16] Early rehabilitation, starting as soon as possible in ICU, is safe and results in better functional outcomes at hospital discharge, a shorter duration of delirium, and more ventilator-free days.[17] In the case of our patient, this was not an alternative until respiratory failure was stabilized and because he had markedly sarcopenia and muscle loss associated with severe critical illness neuromyopathy.

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