

## C A S E R E P O R T

# Vitamin D poisoning; hypercalcemia in a case with richter transformation

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**Abstract.** In addition to modern medicine, the research for complementary and alternative medicine has been conducted for patients with malignancy. In this report, we will present the case of a 52-year-old male patient who presented to the emergency department (ED) with abdominal pain and weakness for 2 days. This patient developed chronic lymphocytic leukemia due to Richter transformation and was diagnosed with vitamin D poisoning that occurred following phytotherapy. In some patients, especially at the ED, treatment of vitamin D toxicity can be challenging. Confusion, polyuria, polydipsia, anorexia, vomiting, and muscle weakness are symptoms of acute poisoning and are related to hypercalcemia. Thus, patients with hypercalcemia should be carefully assessed. Moreover, they should be evaluated for “vitamin D use” rather than “drug use” since families do not consider vitamins as drugs. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** vitamin D poisoning, emergency department, hypercalcemia

## Introduction

In addition to modern medicine, research for complementary and alternative medicine has been conducted for patients with malignancy. With the introduction of modern medicine supplements in phytotherapy, vitamin poisoning cases are encountered in the emergency department (ED).

Vitamin D is a fat-soluble vitamin. Very few foods naturally contain vitamin D (except for oily fish liver); hence, cutaneous synthesis is the primary natural source of vitamin D. Vitamin D from diet or cutaneous synthesis is biologically inactive and converted by enzymes into active metabolites. Liver enzymes convert vitamin D to 25-hydroxyvitamin D (25[OH]D), which is the primary circulating form. In the kidney, vitamin D is converted to 1,25-dihydroxy vitamin D, which is the active form. If high doses of vitamin D are consumed, excess amounts are stored in fat tissues (1). As these areas become saturated, vitamin D remains in the serum, and its conversion

increases 25(OH)D to toxic levels (1). Acute poisoning is linked to hypercalcemia, and symptoms include confusion, polyuria, polydipsia, anorexia, vomiting, and muscle weakness. Chronic poisoning can cause nephrocalcinosis, bone demineralization, and pain.

Chronic lymphocytic leukemia (CLL), the most common type of leukemia in adults, is caused by the accumulation of mature-looking malignant monoclonal B cells in the bone marrow, peripheral blood, or lymph node (2). The clinical spectrum and course of CLL vary, and one-third of the patients live for more than 20 years and require no treatment, while 3%–10% develop aggressive progressive “Richter transformation.” In 1928, Richter transformation was defined by Richter as the most aggressive lymphoma of CLL in a 46-year-old male patient with widespread lymphadenopathy, massive organomegaly, and a rapidly fatal clinical course (1).

Herein, we will present a case of vitamin D poisoning that occurred following phytotherapy of a patient who developed CLL and then Richter transformation.

## Case report

A 52-year-old male patient presented to the ED with abdominal pain and weakness for 2 days. His vital signs were as follows: blood pressure, 130/70 mm/Hg; pulse rate, 107 beats per minute; respiratory rate, 18 breaths per minute; temperature, 36.6°C; and oxygen saturation, 93%. Physical examination findings were normal bilateral breath sounds, abdominal guarding, absence of rebound tenderness, and dry tongue. The patient had CLL for 15 years. He underwent autologous stem cell transplantation, but he developed Richter transformation 6 months ago, recurrence was observed 3 months following transplantation, and treatment was stopped thereafter. He has taken 10 vials of vitamin D (cholecalciferol form) orally for the past 2 months.

Laboratory results are shown in Table 1. 25-Hydroxy vitamin D >100 ng/mL (normal range,

30–100 ng/mL) and chemiluminescence immunoassay total vitamin was examined with D-Roche Diagnostic. In diluted blood, the 25-hydroxy vitamin D level was >150 ng/mL. Laboratory tests performed 6 months ago revealed 9.75 mg/dL of calcium and 0.99 mg/dL of creatinine. Since the patient's 25(OH) D level was >150 ng/mL, which indicated vitamin D poisoning, he developed hypercalcemia and acute renal failure.

Medical treatment was started, and emergency dialysis was planned. His case was consulted with the hematology, nephrology, and intensive care units, and he underwent hemodialysis. After dialysis, blood test values were as follows: urea, 44 mg/dL; creatinine, 1.65 mg/dL; albumin, 2.6 g/dL; sodium, 135 mmol/L; potassium, 2.9 mmol/L; calcium, 11.8 mg/dL (corrected calcium value 12.9 mg/dL). The patient was then admitted in the hematology clinic.

**Table 1.** Hematological parameters of the patient

Hematological Parameters	Results	NR (Normal Range)
Total leukocyte count (WBC)	6500 $\mu$ L	4300-10300 $\mu$ L
Hemoglobin (Hb)	8 g/dL	13.6-17.2 g/dL
Platelet (Plt)	49.900 $\mu$ L	156000-373000 $\mu$ L
Urea	102 mg/dL	17- 49 mg/dl
Creatinine	2.72 mg/dL	0.7-1.2 mg/dL
Uric acid	10.5 mg/dL	3.4-7 mg/dL
Sodium (Na)	131 mmol/L	136-145 mmol/L
Potassium (K)	4 mmol/L	3.5- 5.1 mmol/L
Albumin	2.71 g/dL	3.5-5.2 g/dL
Calcium (Ca) Corrected Calcium Value (CCV)	16.3 mg/dL 17.33 mg/dL	8.4-10.2 mg/dL
Total Protein	4.91 g/dL	6.4-8.3 g/dL
Phosphorus (P)	4.43 mg/dL	2.5 -4.5 mg/dL
Parathormon(PTH)	2.14 pg/mL	15-65 pg/mL
C-Reactive Protein (CRP)	166 mg/L	<5
Arterial Blood Gas pH Lactat	7.41 2.7 mmol/L	7.35-7.45 0.5-1.6 mmol/L
25-Hydroxy Vit-D (25 (OH) D) Diluted and repeated value	> 100 ng/mL >150 ng/mL	30-100 ng/mL

## Discussion

Dieticians often use high-dose vitamin D supplements in patients with malabsorption syndrome, renal osteodystrophy, osteoporosis, or psoriasis. Vitamin D poisoning has been documented in adults receiving more than 60,000 IU per day (1). Cases with hypervitaminosis D due to accidental intake of products containing high doses of vitamin D and prescription errors were reported (1). Prolonged exposure to sunlight does not cause vitamin D<sub>3</sub> (cholecalciferol) poisoning, because precursor vitamin D<sub>3</sub> and vitamin D<sub>3</sub> are inactive metabolites and need to be converted to active forms (1). Many studies suggest that prolonged exposure of the skin to sunlight would only produce a maximum serum 25(OH)D level of <80 ng/mL (200 nmol/L) (1).

There are two forms of vitamin D: vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol). The first step in the synthesis of vitamin D<sub>3</sub> is the conversion of provitamin D in the skin to vitamin D<sub>3</sub> (cholecalciferol) under the influence of the sun or ultraviolet rays. Vitamin D<sub>3</sub> is transported to the liver, where it is activated by one of a series of 25-hydroxylases—major enzymes are microsomal CYP2R1 and mitochondrial CYP27A1. Its product, 25-hydroxyvitamin D<sub>3</sub> [25(OH)D<sub>3</sub>], is then carried by vitamin D binding protein (DBP) to the kidney, where the classic renal CYP27B1 1-hydroxylates it and puts it back into the circulation as 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>]. 1,25(OH)<sub>2</sub>D<sub>3</sub> then enters and acts on vitamin D target cells at the level of gene transcription through a vitamin D receptor-mediated mechanism. In hypervitaminosis D, some researchers argue that saturation of the DBP displaces a greater amount of free 1,25(OH)<sub>2</sub>D<sub>3</sub>, thereby increasing gene expression and causing hypercalcemia and other toxicity symptoms. Advanced hydroxylation of 25OHD to 1,25-dihydroxyvitamin D (1,25OHD) occurs in the mitochondria of the proximal tubules of the kidneys. 1,25OHD is the physiologically active form of vitamin D (3,4,5).

The recommended intake of vitamin D through diet for adult men and women (including during pregnancy and breastfeeding) aged 19–75 years is 600 IU/day and those aged >75 years is 800 IU/day. The tolerable upper level is 4000 IU in these age groups.

Pharmaceutical preparations contain 300,000 IU/mL (3). In the present case, the patient drank 10 ampules of vitamin D within 2 months. One vial of vitamin D preparation contains 300,000 IU. When calculated, the patient drank 10 × 300,000 IU of vitamin D. Even if the patient had severe vitamin D deficiency (if serum levels were less than 10 ng/mL), his treatment would have been 50,000 IU/week for 6–8 weeks, with a tolerable upper level of 4000 IU per day. Serum 25(OH)D levels can reach 150 ng/mL or above, and vitamin D toxicity can occur by taking daily values higher than 10,000 IU (4). In the present case, taking 3 million IU of vitamin D in 2 months caused hypercalcemia and acute renal failure due to vitamin D toxicity.

The liver is a typical storage system for vitamin D. When taking large amounts of vitamin D, excess amounts are stored in fat tissues (1). As these areas become saturated, vitamin D remains in the serum and then converted, reaching toxic levels of 25(OH)D. In the present case, since the patient has consumed high doses of vitamin D for a long time, his vitamin D level in the blood was >150 ng/dL for approximately 20 days. Although the patient was on both medical treatment and regular dialysis, his vitamin D level was above 150 ng/dL even on the 20th day of follow-up, because he had excessive amounts of vitamin D stored in the adipose tissues. After the first month, his vitamin D level in the diluted blood was at 138 ng/dL.

In vitamin D intoxication, excessive serum 25(OH)D level increases the risk for hypercalcemia and hypercalciuria by increasing intestinal calcium reabsorption and calcium mobilization from the bones. The serum calcium level is below 12 mg/dL in mild hypercalcemia, 12–15 mg/dL in moderate hypercalcemia, and >15 mg/dL in severe hypercalcemia (5). While mild hypercalcemia may be asymptomatic, moderate to severe hypercalcemia may be associated with various symptoms. Severe hypercalcemia is almost always symptomatic. It occurs suddenly and mostly associated with malignancies (6). Upon admission, our patients' calcium level was 16.3 mg/dL (corrected Ca value of 17.33 mg/dL), which indicated severe hypercalcemia.

Patients show gastrointestinal symptoms such as nausea, vomiting, anorexia, constipation, abdominal pain, pancreatitis in rare cases, and peptic ulcer disease (7). Moreover, neurological signs can range from fatigue

to coma, anxiety, cognitive dysfunction, and psychiatric conditions such as depression, as well as cardiovascular symptoms, including arrhythmias and shortening of the QT interval (8). Renal dysfunction may develop with polyuria compatible with nephrogenic diabetes insipidus due to hypercalcemia (8). Although the serum creatinine levels of our patient were normal 3 months ago, acute renal failure was detected in the ED. As our patient did not have chronic renal failure, acute renal failure could be also attributed to vitamin D intoxication. Nausea and weakness increase dehydration with reduced oral fluid intake. Our patient also had dehydration, weakness, and abdominal pain due to hypercalcemia, consistent with the literature.

In patients with lymphoma, overproduction of extrarenal 1,25-dihydroxy vitamin D causes hypercalcemia, which suppresses parathyroid hormone, and serum 1,25-dihydroxy vitamin D may increase without an elevation in serum 25(OH)D level (1). In our patient, this was thought to contribute to hypercalcemia. A calcium level of 16.3 mg/dL (corrected calcium value, 17.33 mg/dL) in the blood at the time of admission is considered severe hypercalcemia.

## Conclusions

In some patients, establishing a history of consuming high doses of vitamin D can be very difficult. Patients with hypercalcemia should be carefully assessed and evaluated for “vitamin D use” rather than “drug use” because families do not consider vitamins as drugs. In the present case, the complaints of abdominal pain and weakness could be considered as a metabolic event related to malignancy.

In conclusion, although the unconscious and uncontrolled use of vitamin preparations is widespread, the use of vitamin D should be questioned in cases presenting with nonspecific complaints that are considered intoxication in the ED. With the proliferation of complementary and alternative medicine in patients with malignancy, patients who need vitamin D and who have started treatment should be clinically evaluated and laboratory results monitored. Patients

with fat-soluble and stored vitamin toxicity may require long-term follow-up, treatment, and dialysis.

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