J Tokyo Wom Med Univ
79 (11) 455～462 (2009)

Report

Hypercalcemic Crisis in an Osteoporotic Patient Taking a Maintenance Dose of 1α-hydroxyvitamin D_3 with an Unsuppressed Serum Level of Intact PTH

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(Accepted Aug. 20, 2009)

A 70-year-old osteoporotic woman taking a maintenance dose of 1α-OHD_3 (0.75 μg/day) developed acute hypercalcemic crisis associated with acute renal failure (serum creatinine 3.4 mg/dl). Extensive examination revealed no abnormality except for several intrathyroidal nodules. Three days after admission, saline infusion had reduced the serum calcium concentration from 15.6 to 14.5 mg/dl, but the serum intact PTH concentration was not suppressed (14 pg/ml, reference range 10-65 pg/ml). A single administration of alendronate reduced the serum calcium and creatinine levels to the normal ranges. Two years later, mild hypercalcemia (11.3 mg/dl) with complete suppression of the serum level of intact PTH (<5 pg/ml) occurred due to inadvertent intake of 1,25-$(OH)_2D_3$ (1.0 μg/day). After discontinuation of 1,25-$(OH)_2D_3$, the patient remained eucalcemic until she died aged 78 years. Although hypercalcemic crisis with acute renal failure due to acute vitamin D intoxication was highly suspected, previous reports have documented decreases in serum intact PTH to below the detectable range (<5 pg/ml) in similar cases. We discuss the pathogenesis of unsuppressed serum intact PTH, and stress that in hypercalcemic patients, the serum level of intact (or whole) PTH should be determined immediately at the hypercalcemia peak.

Key words: hypercalcemic crisis, PTH, primary hyperparathyroidism

Introduction

Hypercalcemic crisis develops most frequently in patients with primary hyperparathyroidism (P-HPT) and malignancy due to excessive production of PTH and PTHrP, respectively. In some cases, hypercalcemic crisis may develop due to excessive intake of vitamin D and its analogue. Usually, diagnosis is not difficult when a detailed medical history is available, and serum levels of PTH, PTHrP, and vitamin D metabolites are measured[1]. However, when hypercalcemic crisis resolves spontaneously and completely disappears[2)~12)], differential diagnosis is sometimes difficult, particularly if serum levels of PTH and vitamin D metabolites are not measured when the serum calcium concentration is maximal.

Here we report a patient with senile osteoporosis who had intrathyroidal nodules and was receiving a daily maintenance dose of 0.75 μg 1α-hydroxyvitamin D_3 (1α-OHD_3), who acutely developed hypercalcemic crisis. Although vitamin D intoxication was the most likely diagnosis in the present case, the patient had been constantly taking a daily maintenance dose of 0.75 μg 1α-OHD_3, which is within the safe recommended range for osteoporosis (0.5-1.0 μg/day)[13]. If a healthy patient with senile osteoporosis in the absence of renal dysfunction were to develop hypercalcemic crisis solely by taking such

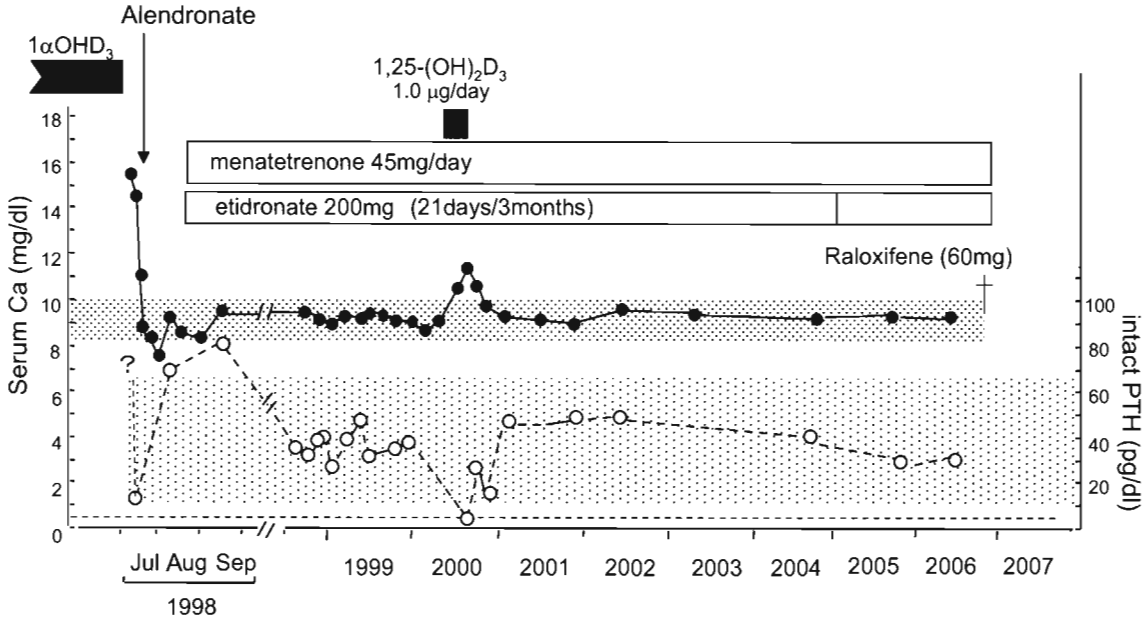

Fig. 1 Clinical course of the patient with hypercalcemic crisis of undetermined origin
Dotted areas indicate the normal ranges of calcium (8.5-10.0 mg/dl) and intact PTH (10-65 pg/ml) levels. Serum calcium levels (mg/dl)(●—●), intact PTH (○—○). Dotted line indicates the sensitivity of the PTH assay (<5 pg/ml).

a dose of 1α-OHD_3, it would be a grave concern for numerous patients with osteoporosis. Therefore, we investigated whether additional aggravating factor (s) may have been involved in the development of acute hypercalcemic crisis.

Case Reports

An otherwise healthy woman (born in 1919) with senile osteoporosis and hypertension had been taking 1α-OHD_3 (0.75 μg/day, Alfarol, Chugai Pharmaceutical Co. Tokyo), calcium lactate (3 g/day), and calcium-blockers for several years. At the beginning of July 1998, lumbago developed and the patient was confined to bed. In a few days, she became confused and disoriented, and was admitted to an affiliated hospital of Tokyo Women's Medical University in mid July. The patient had been completely compliant with the dose of medication and denied any further prescription including vitamin D, vitamin A, thiazide diuretics, thyroid hormone or additional calcium supplements. On admission, she was unconscious and dehydrated. The serum levels of calcium, phosphate and albumin were 15.6 mg/dl, 4.8 mg/dl, and 4.0 g/dl, respectively. Biochemical data were not remarkable except for increased serum levels of BUN (61.0 mg/dl) and creatinine (4.3 mg/dl). Unfortunately, the serum levels of intact PTH and 1,25-$(OH)_2D$ were not determined on the first day of admission. After administration of saline, the serum calcium level decreased slightly to 14.5 mg/dl on the third hospital day, but the serum level of intact PTH remained within the lower normal range (14 pg/ml, reference range 10-65 pg/ml), whereas that of mid-regional PTH fragments (highly sensitive PTH, HS-PTH, Yamasa Shoyu Diagnostics, Noda, Japan) was elevated to 1,000 pg/ml (reference range 160-520 pg/ml).

After administration of a single dose of 10 mg alendronate (Onclast, Merck-Banyu, Tokyo), the serum level of calcium decreased steadily, reaching 7.5 mg/dl on the ninth hospital day, accompanied by amelioration of renal function (BUN 19.4 mg/dl, creatinine 1.4 mg/dl). The patient's renal function normalized completely in early August. On the thirteenth hospital day, when the serum calcium level had become normal (9.2 mg/dl), the serum level 25-OHD was also normal (10.1 ng/ml, reference range; 9.0-33.9 ng/ml) and that of 1,25-$(OH)_2D$ was decreased to 11 pg/ml (reference range; 27.5-68.7 pg/ml). Serum levels of intact PTH and HS-PTH were transiently increased to 69 pg/ml and 1,290 pg/ml,

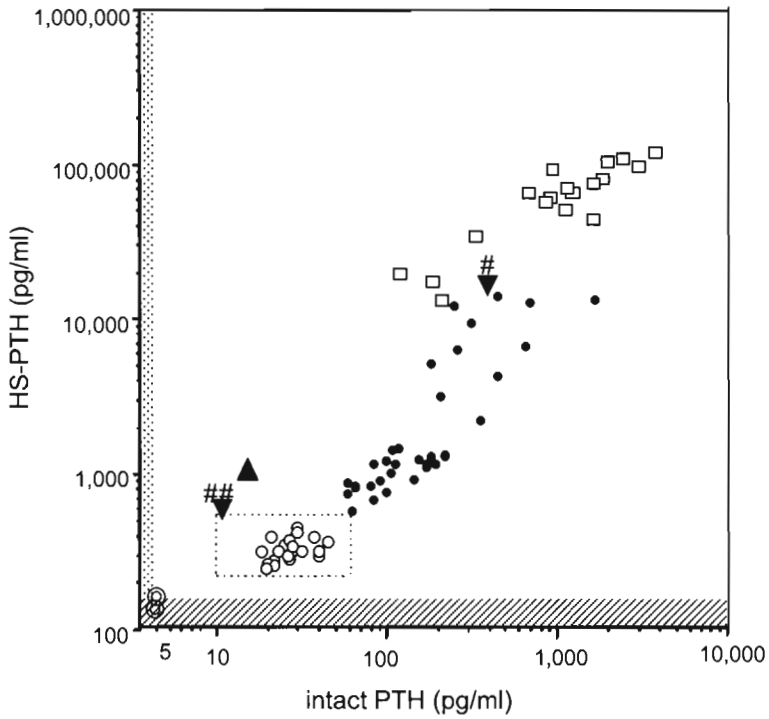

Fig. 2 Relationship between intact PTH and HS-PTH

Intact PTH and HS-PTH were determined in the same samples in 20 normal subjects, patients with idiopathic hypoparathyroidism (n=2), I°-HPT (n=32) and II°-HPT (n=18), the present patient after the hypercalcemic crisis (▲), and a patient with hyperparathyroidism who developed spontaneous infarction of the parathyroid adenoma (▼)(# at the time of hypercalcemic crisis, ## in the hypocalcemic phase)[7]. Dotted line indicates reference ranges of PTH. Shaded areas indicate the undetectable range (intact PTH <5 pg/ml, HS-PTH <160 pg/ml). ○: normal subjects. ◎: idiopathic hypoparathyroidism, ●: I°-HPT, □: II°-HPT.

respectively. The serum level of the N-terminal fragment of PTHrP was not detectable (<1.1 pmol/L). Radiographic studies revealed no malignant lesion. For further evaluation, the patient was referred to our hospital in August, 1998.

The patient, who had kyphosis, was 132 cm in height and weighed 51.2 kg. Serum levels of albumin calcium, phosphate, BUN and creatinine were 3.7 g/dl, 9.2 mg/dl, 3.6 mg/dl, 11.7 mg/dl, and 0.86 mg/dl, respectively. The estimated glomerular filtration rate [eGFR] according to the calculation formula proposed by the Japan Nephrology Society was about 73 ml/min. The patient had no proteinuria, glucosuria or hematuria. Ultrasonographic examinations of the cervical region performed by an experienced physician demonstrated several adenomatous nodules in the thyroid gland (27.0 × 23.7 × 17.4 mm in the central region and several 4-12 mm nodules in the both lobes), but visualized no lesion suggestive of a parathyroid adenoma. Although an intrathyroidal parathyroid adenoma was suspected[14], color flow Doppler sonography revealed no hypervascular lesion. Despite extensive radiological examinations (systemic CT scans and MRI), no abnormal lesion suggesting parathyroid adenoma was detected in the cervical and thoracic region. Furthermore, ^{99m}Tc-MIBI scan demonstrated no suspicious findings. Under a tentative diagnosis of hypercalcemic crisis of undetermined origin, the patient was prescribed menatetrenone (45 mg/day, Grakay, Eizai Pharmaceutical Co., Tokyo, Japan)[15], etidronate (200 mg for 14 days per 3 months), amlodipine (5 mg) and pravastatin (10 mg), and visited the outpatient clinic monthly.

In summer 2000, the serum level of calcium increased to 11.6 mg/dl, accompanied by a completely suppressed level of intact PTH (<5 pg/ml). Although malignancy-associated hypercalcemia was suspected, anamnesis revealed that the patient had visited a local physician and had been prescribed

Table Case reports of vitamin D intoxication with acute renal failure

	Vitamin	Age (sex)	Serum Ca (mg/dl)	P (mg/dl)	Creatinine (mg/dl)	PTH (pg/dl)	25-OHD (ng/ml)	1.25-$(OH)_2D$ (pg/ml)	Reference
1.	D_3	63 (m)	15.3 (8.8-10.6)	ND	5.0 (0.68-1.3)	< 1 pmol/L (1.3-7.6)	592 (7.6-30.5)	60.1 (12-56)	23
2.	D_3	3M (m)	18.5 (8.9-10.1)	3.2 (3.6-5.5)	ARF	< 1 pg/ml (8-74)	360 (10-40)	ND	24
3.	D+A	62 (m)	15.3	ND	3.72	1.3 pg/ml	> 150	32.5	25
		55 (f)	11.3		1.8	2.5 pg/ml (14-60)	> 150 (16-74)	47.9 (14-60)	
4.	D_3	6M (f)	16.8 (9-11)	6.0 (4.5-6.5)	ARF	1 pg/ml (8-70)	340 (10-50)	44 (25-45)	26
5.	D	16M (m)	18.0 (8.8-10)	3.4 2.2-3.8	ARF	< 4 (10-55)	672 (25-80)	110 (22-67)	27
6.	OCT	55 (m)	13.7	ND	2.5	< 4 pg/ml	ND	30.9	28
7.	OCT	53 (m)	13.8	4.4	3.7	< 5 pg/ml	ND	16.0	29
8.	(−)*	40 (f)	13.1	ND	3.4	< 5 pg/ml (10-60)	ND	120.7 (20-60)	30
9.	(−)*	56 (m)	16.0 (8.24-10.4)	ND	4.4 (0.89-1.70)	3.4 (< 50)	24.7 (7.6-41.9)	111 (15.9-59.7)	31

D_3: cholecalciferol, A: vitamin A, OCT: 22-oxacalcitriol, (−)*: patients with sarcoidosis without VD supplementation.
M: months, m: male, f: female, ND: not described, ARF: acute renal failure. Parentheses indicate reference range.

1α, 25-$(OH)_2D_3$ (rocaltrol, Chugai Pharmaceutical Co.) at a daily dose of 0.5 μg/day, which the patient had taken twice daily (1.0 μg/day). The serum level of 1,25-$(OH)_2D$ was increased to 65 pg/ml (reference range 20-60 pg/ml). After withdrawal of 1,25-$(OH)_2D_3$, the hypercalcemia disappeared immediately (Fig. 1), and the level of intact PTH increased to 14 pg/ml (HS-PTH level was 190 pg/ml) in two weeks, confirming that this hypercalcemia had been due to vitamin D intoxication.

Since then, the patient's clinical course has been uneventful, and the serum levels of calcium, phosphate, and intact PTH have remained within the normal ranges for the last 8 years. A number of pancreatic pseudocysts that developed at the time of acute hypercalcemic crisis disappeared completely[16]. In 2004, ultrasonographic studies revealed that the largest nodule remained unchanged in size but a couple of the nodules 4-6 mm in diameter could not be identified. The patient debilitated by age and passed away at the end of 2006.

Results

Since intact PTH was not suppressed in the present patient despite marked hypercalcemia, we measured the serum level of PTH using both an intact PTH assay kit (Nichols Institute, USA) and a HS-PTH assay kit (Yamasa Diagnostics, Chiba, Japan) at the same time in normal subjects (n = 20), idiopathic hypoparathyroidism (n = 2), and patients with I°-HPT (n = 20) and II°-HPT (n = 18). The former kit measures mainly intact PTH (PTH 1-84) including the C-terminal fragment (PTH 7-84)[17]. Serum samples were stored at −20℃ and analyzed simultaneously using the HS-PTH assay kit[18]. This assay kit uses an antibody (CH9) supplied by Slatopolsky et al. and measures mainly mid-regional PTH fragments[19]. Although the precise PTH fragments recognized by the antibody are not specified, they have a longer half-life (1-2 h)[20] than intact PTH (2-3 min)[1].

Serum levels of intact PTH and HS-PTH in normal subjects, patients with hypoparathyroidism and hyperparathyroidism, and 2 patients with hypercalcemic crisis

As shown in Fig. 2, there was a good correlation between the serum levels of intact PTH and HS-PTH in normal subjects and patients with I°-HPT ($y = 10.3x + 179$). In normal subjects and patients with I°-HPT, the HS-PTH/intact PTH ratio was 9.7 ± 2.2 (n = 20) and 11.8 ± 7.0 (n = 32, mean ± SD) re-

spectively, whereas it was increased to 55.8 ± 26.7 in patients with Π°-HPT (n = 18). It is noteworthy that the level of intact PTH was within the lower normal range (14 pg/ml) despite marked hypercalcemia (14.5 mg/dl) in the present patient. The increased ratio (71.4) of HS-PTH (1,000 pg/ml) to intact PTH (14 pg/ml) would have been due to renal dysfunction associated with the hypercalcemic crisis, since half-life of mid-regional PTH fragments was more prolonged than that of intact PTH.

An increased ratio (56.3) of HS-PTH (620 pg/ml) to intact PTH (11 pg/ml) was also found in a 67-year-old woman with primary hyperparathyroidism on the day of admission to our hospital (Fig. 2), when renal function had become completely normal (BUN 9.2 mg/dl, creatinine 0.80 mg/dl). This patient had developed hypercalcemic crisis (serum calcium 15.2 mg/dl) with acute renal failure due to complete infarction of a parathyroid adenoma (intact PTH 344 pg/ml, HS-PTH 12,900 pg/ml)[7].

Discussion

Usually, the most likely diagnosis in an osteoporotic woman who has been continuously taking 1α-OHD_3 and calcium is vitamin D intoxication[13]. However, the patient had been constantly compliant with a maintenance dose of 1α-OHD_3 (0.75 μg/day) and oral calcium (0.55 g/day). Usually, osteoporotic women are prescribed 1α-OHD_3 at a daily dose of 0.5-1.0 μg. Although mild to moderate hypercalcemia is sometimes evident at these doses in osteoporotic patients with renal failure, hypercalcemia is rare in those with normal renal function. According to Chugai Pharmaceutical Co. (Tokyo, Japan), more than 12 million people with postmenopausal and senile osteoporosis have been prescribed 1α-OHD_3 at a daily maintenance dose of 0.5-1.0 μg since 1981. However, there has been no published case report of 1α-OHD_3 at a daily dose of 0.75 μg/day causing hypercalcemic crisis in osteoporotic patients with normal renal, hepatic and cardiac function. Therefore, it is very reasonable to speculate that some additional factor(s) may have been involved in the development of acute hypercalcemic crisis in the present patient.

Since 1,25-$(OH)_2D_3$ suppress PTH release at the transcriptional level, serum level of PTH is generally decreased to undetectable level in patients with vitamin D intoxication. Indeed, the serum level of intact PTH had decreased to below the normal or detectable range in all patients with various forms of vitamin D intoxication associated with acute renal failure who recovered from it completely[21)~31)] (Table). This was also the case in patients with psoriasis vulgaris treated topically with massive 2-oxacalcitriol (a vitamin D analogue)[28]. In such a hypercalcemic patient (13.8 mg/dl) with renal failure (creatinine 3.7 mg/dl), the serum level of intact PTH was suppressed to <5 pg/ml, and HS-PTH was also decreased to the lower end of the reference range (210 pg/ml)[29] (personal communication from Dr. Nakayama M, Chubu Rosai Hospital). Furthermore, in a hypercalcemic patient with sarcoidosis due to overproduction of 1,25-$(OH)_2D$, in whom the serum levels of calcium and creatinine increased to 13.1 mg/dl and 3.4 mg/dl, respectively, the serum level of intact PTH was suppressed to < 5 pg/ml[30]. Therefore, the second hypercalcemia that developed in August 2000 was undoubtedly due to vitamin D intoxication, since serum levels of 1,25-$(OH)_2D$ and intact PTH were increased and suppressed to undetectable range, respectively.

In contrast to the second hypercalcemia, serum level of intact PTH was not suppressed at the first hypercalcemia. One of possible reasons for unsuppressed serum level of intact PTH despite of severe hypercalcemia is the hysteresis phenomenon, in which PTH is secreted at a slightly hypercalcemic level during the period when hypercalcemia is resolving[32], however, it could not account for the non-suppressed serum level of intact PTH (14 pg/ml), since the observed threshold for PTH secretion during the period when serum calcium is decreasing is only around 2.75 mmol/L (11 mg/dl) in patients with hypercalcemia receiving bisphosphonate[33].

The non-suppressed serum level of intact PTH together with an increased level of mid-regional PTH fragments suggests that, despite marked hypercalcemia, a slightly excessive release of intact PTH was still present on the third hospital day. Therefore, although we were unable to demon-

strate any distinct parathyroid lesion in the present patient, it is possible that the hypercalcemia may have become acutely exacerbated due to complete infarction of an unidentified parathyroid adenoma. The increased ratio (71.4) of HS-PTH (1,000 pg/ml) to intact PTH (14 pg/ml) is compatible with renal dysfunction associated with hypercalcemic crisis, since the half-life of HS-PTH is 30 times longer than that of intact PTH (2-3 min)[1].

It should be pointed out that, although the patient developed lumbago and was confined to bed as initial symptoms in July 1988, hypercalcemia due to immobilization[34] is unlikely for the following reasons. First, the syndrome usually develops in children, adolescents, and young adults with high bone turnover who are immobilized due to spinal cord injury or large bone fractures. Secondly, serum levels of intact PTH are completely suppressed to less than 2 pg/ml at the time of immobilization hypercalcemia[35][36].

Although vitamin D (1α-OHD_3) was certainly at least partly involved in the development of hypercalcemic crisis in the present patient, we speculate that additional aggravating factor(s) may have been involved. We speculate that one possibility was spontaneous and complete infarction of parathyroid adenoma that could not be detected by radiological or ultrasonographic examinations. Although a couple of nodular lesions (4-6 mm) within the thyroid gland were undetectable after 10 years, adenomatous nodules frequently degenerate and decrease in size[37], although intrathyroidal parathyroid adenoma could not be completely excluded[14]. Presumably, transient excess PTH release together with oral intake of 1α-OHD_3 and calcium may have acutely and synergistically increased the serum calcium concentration, leading to acute hypercalcemic crisis in the present patient. Although this scenario is highly speculative, it should be stressed that when hypercalcemic patients are admitted, serum levels of intact (or whole) PTH should be determined immediately at the peak of hypercalcemia, or before the acute hypercalcemia begins to ameliorate or has completely disappeared.

Acknowledgments

We thank Dr. Nakayama M (Chubu Rosai Hospital, Nagoya) for providing unpublished data. This work was partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (# 20591102).

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維持量の活性型ビタミンD（1α-OHD_3）を内服中にintact PTH抑制が不十分な高カルシウム血症クリーゼを呈した骨粗鬆症患者の一例

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本邦で開発された活性型ビタミン（VD）（1α-OHD_3）は，これまで4半世紀以上にわたり安全に骨粗鬆症患者に使用されている．しかし，当院では常用量の1α-OHD_3（0.75 μg/day）を長年にわたり内服していたところ，急性腎不全［血清クレアチニン（Cr）3.4 mg/dl］を伴う高カルシウム（Ca）血症クリーゼ（血清Ca値15.6 mg/dl）を生じた1症例を経験したので報告する．昏睡状態で入院した後，全身的に精査するも甲状腺内に複数の結節を認めるほかには特に異常所見を認めなかった．入院後直ちに生理的食塩水を点滴静注し，3日後（血清Ca 14.5 mg/dl）に測定した血中intact PTHは14 pg/ml（正常値10～65 pg/ml）であった．Alendronate点滴静注後，血清Ca値もCr値も速やかに正常化した．退院後は平穏に暮らしていたが，2年後に再び高Ca血症（11.3 mg/dl）が生じてきた．Intact PTHは5 pg/ml以下に抑制されており，近医で処方された1,25$(OH)_2D_3$の過剰摂取（1.0 μg/day）による軽度のVD中毒であることが判明した．1,25$(OH)_2D_3$中止後は，78歳で老衰死するまで血清Ca値は常に正常範囲であった．最初の高Ca血症クリーゼの成因として，一応VD（1α-OHD_3）中毒が疑わしいが，0.75 μg内服による報告例は見あたらない．また，これまで報告された急性VD中毒症例ではすべてintact PTHが5 pg/ml以下に抑制されていたことを考慮すると，高Ca血症クリーゼの一因として本症例では一過性のPTH過剰分泌（例，副甲状腺腫の自然梗塞など）が関与していた可能性も完全には否定できない．いずれにしても，高Ca血症患者を診た場合には，入院当日（高Ca血症のピーク時）に血清Ca，リン，およびintact PTHを測定しておくことが重要である．