

[CASE REPORT]

Hypercalcemia Associated with the Ectopic Expression of 25-hydroxyvitamin D3-1 α -hydroxylase in Diffuse Large B-cell Lymphoma

Masashi Ogawa¹, Maho Morikawa¹, Masaki Kobatake¹, Taku Murakami¹, Yuki Yamamoto²,
Rikiya Watanabe³, Katsumi Yamada³, Katsuhito Nishiyama¹,
Yoshiro Yasutomo¹ and Kenta Hara¹

Abstract:

An 82-year-old man was transferred to our hospital due to impaired consciousness. His albumin-corrected calcium level was 14.2 mg/dL, intact parathyroid hormone (PTH) and PTH-related protein levels were reduced, and his 1,25-dihydroxyvitamin D [1,25(OH)₂VitD] level was elevated at 71.5 pg/mL. Computed tomography revealed masses on the bilateral ribs. The mass on the rib was biopsied and diagnosed as diffuse large B-cell lymphoma (DLBCL). Immunostaining of the biopsy sample with the anti-CYP27B1 antibody revealed the ectopic expression of 1 α -hydroxylase in the lesion. We herein report a rare case of hypercalcemia induced by the overproduction of 1,25(OH)₂VitD in DLBCL ectopically expressing 1 α -hydroxylase.

Key words: calcium, 1,25(OH)₂VitD, 1 α -hydroxylase, CYP27B1, lymphoma

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Introduction

Hypercalcemia is one of the most common metabolic complications associated with neoplastic disease. It has been estimated to occur in 3% to 30% of all cancer patients (1-3). Hypercalcemia often leads to life-threatening metabolic disorders, including progressive mental impairment and acute renal failure.

Two major mechanisms have been reported for malignancy-related hypercalcemia. The main mechanism, accounting for approximately 80% of cases, is mediated by the production of parathyroid hormone (PTH)-related peptide (PTHrP) and is recognized as humoral hypercalcemia of malignancy (HHM). The second mechanism, which occurs in approximately 20% of cases, involves osteolytic metastases and excessive calcium release from bone and thus is known as local osteolytic hypercalcemia (LOH). Minor mechanisms, accounting for less than 1% of cases of

malignancy-related hypercalcemia, involve the overproduction of the active form of vitamin D, 1-alpha, 25-dihydroxyvitamin D3 [1,25(OH)₂VitD], or PTH; in the former case, tumor cells or adjacent macrophages ectopically express 1 α -hydroxylase, thereby overproducing 1,25(OH)₂VitD, while in the latter case, authentic PTH is overproduced by parathyroid carcinoma or ectopically secreted by PTH-producing cancers (4, 5).

Lung and breast cancers are the most common types of malignancy among the tumor types causing hypercalcemia, with hypercalcemia occurring in approximately 24-28% of these cancers (2). Among cases of hematopoietic malignancies, hypercalcemia may occur in multiple myeloma mostly through LOH (3). Hypercalcemia also sometimes occurs in patients with leukemia or malignant lymphomas, but to a lesser extent than in those with multiple myeloma (4). The mechanism accounting for these cases is mediated by the secretion of PTHrP mostly by human T-cell lymphotropic retrovirus type 1 infection-associated leukemia/lymphoma or

¹Department of Diabetes and Endocrine Disease, Kita-Harima Medical Center, Japan, ²Department of Diagnostic Pathology, Kita-Harima Medical Center, Japan and ³Department of Internal and Geriatric Medicine, Kita-Harima Medical Center, Japan

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Correspondence to Dr. Kenta Hara, harakkobe@gmail.com

non-Hodgkin's lymphoma (4, 5). While PTHrP-mediated hypercalcemia is characterized by low levels of $1,25(\text{OH})_2\text{VitD}$ and metabolic alkalosis, rare cases of hypercalcemia inducing the overproduction of $1,25(\text{OH})_2\text{VitD}$ have been reported in patients with lymphomas (6-11). However, evidence to support the excessive synthesis of $1,25(\text{OH})_2\text{VitD}$ by the ectopic expression of 25-hydroxyvitamin D3- 1α -hydroxylase (1α -hydroxylase) in malignant lymphomas is limited (12-14).

We herein report a case of hypercalcemia associated with diffuse large B-cell lymphoma (DLBCL) caused by the overproduction of $1,25(\text{OH})_2\text{VitD}$. We demonstrated that lymphoma cells were positive for 1α -hydroxylase (CYP27B1), indicating that the overproduction of $1,25(\text{OH})_2\text{VitD}$ was caused by the ectopic expression of 1α -hydroxylase in lymphoma cells.

Case Report

An 82-year-old man was transferred to our hospital from a rehabilitation hospital due to a loss of appetite and impaired consciousness. The patient had been relatively well and had not been bedridden approximately four days previously, when he began to lose his appetite and gradually became somnolent. He had histories of hypertension, chronic kidney disease, chronic thyroiditis, and diabetes mellitus and had been prescribed candesartan (8 mg/day), levothyroxine (12.5 $\mu\text{g}/\text{day}$), mitiglinide (15 mg/day), and teneligliptin (20 mg/day) but not medications such as vitamin D, vitamin A, thiazide diuretics, or lithium carbonate.

On admission, his conscious level was impaired with a Glasgow Coma Scale of E2V1M5. His blood pressure was 173/88 mmHg, pulse rate was regular at 83 beats per minute, body temperature was 36.2°C , and respiratory rate was 21 breaths per minute. A physical examination revealed a 4-cm immobile hard mass in the left anterior chest, and respiratory sounds were decreased in the lower field of the left lung. His thyroid gland was elastic-soft with no swelling or nodules. Cardiac sounds were normal, and an abdominal examination revealed no abnormalities. Lymph nodes were not swollen in the neck upper clavicular, axillar, or inguinal region.

Laboratory tests on admission showed high values for serum albumin-corrected calcium (cCa), 14.2 mg/dL (calcium 13.0 mg/dL, albumin 2.8 g/dL); ionized calcium (iCa), 1.66 mmol/L; phosphate, 5.5 mg/dL; blood urea nitrogen (BUN), 75.3 mg/dL; and creatinine, 4.68 mg/dL, and decreased estimated glomerular filtration rate (eGFR) of 10 mL/min/1.73 m^2 (Table). Serum levels of ammonia and glucose were within normal ranges. Since there were no clinical signs of infection or intracranial disease, hypercalcemia and (at least in part) uremia were considered to be the causes of his impaired consciousness.

Regarding the cause of hypercalcemia, the medical history of the patient excluded the possibility of drug-induced hypercalcemia. Since the values for free-T4, thyroid stimulat-

ing hormone (TSH), and the κ/λ ratio were within normal ranges and serum protein electrophoresis was also normal, neither hyperthyroidism nor multiple myeloma were considered to be the cause of hypercalcemia. Familial hypocalciuric hypercalcemia was also excluded because the fractional excretion of calcium was 10.9%. In contrast to the elevated level of calcium, intact PTH was at the lower end of the normal range at 17 pg/mL (10-65 pg/mL), and PTHrP was not elevated at <1.0 pmol/L (≤ 1.1 pmol/L). However, the level of $1,25(\text{OH})_2\text{VitD}$ was elevated at 71.5 pg/mL (20-60 pg/mL) despite hypercalcemia and end-stage kidney disease, whereas the level of 25-hydroxyvitamin D3 [$25(\text{OH})\text{VitD}$] was slightly low at 18.1 ng/mL (≥ 20 ng/mL) (Table). Therefore, the overproduction of $1,25(\text{OH})_2\text{VitD}$ was considered to be the cause of hypercalcemia.

Computed tomography of the body revealed a well-defined nodule in the middle lobe of the right lung, masses with osteolytic changes on the left 5th and right 6th and 7th ribs, and a soft tissue mass along the pericardium (Fig. 1).

Since the soluble interleukin-2 (IL2) receptor was elevated at 6,260 U/mL, malignant lymphoma was suspected. A biopsy was performed on the soft mass lesion of the left 5th rib. Hematoxylin & eosin staining of the biopsy sample revealed diffuse atypical lymphocytes with nuclei of different sizes (Fig. 2a, b), and the immunostaining of samples revealed positive cells for CD20 and Ki67 in a large number of these lymphocytes (Fig. 2c, d). The Ki67 index was over 70%. Based on these results, the patient was diagnosed with DLBCL. Since the overproduction of $1,25(\text{OH})_2\text{VitD}$ was considered the cause of hypercalcemia, the ectopic expression of 1α -hydroxylase in these lesions was suspected. To confirm this, an antibody against CYP27B1, whose gene expression results in 1α -hydroxylase, was purchased from Abcam (#EPR20271; Discovery Drive, Cambridge, Biomedical Campus, Cambridge, UK), and immunostaining of the biopsy sample with the antibody was performed. The results obtained confirmed that lymphoma cells in the tissue sample were positive for CYP27B1 (Fig. 3a), indicating that 1α -hydroxylase was ectopically expressed in the lesion.

To treat the patient's hypercalcemia, 2,000 mL/day of saline, 40 units of elcatonin twice a day, and 4 mg of zoledronic acid were administered on the first day (Fig. 4). The infusion of saline was gradually reduced over seven days, and the administration of elcatonin was completed after three days. Serum levels of cCa and iCa decreased to 13.1 mg/dL and 1.52 mmol/L, respectively, on the second day, and these values decreased further to 11.8 mg/dL and 1.37 mmol/L, respectively, on the third day after admission. The consciousness level improved accordingly but worsened again on day 13 as the serum levels of cCa and iCa increased to 12.4 mg/dL and 1.39 mmol/L, respectively. To inhibit the 1α -hydroxylase-mediated conversion of $25(\text{OH})\text{VitD}$ to $1,25(\text{OH})_2\text{VitD}$, the continuous intravenous infusion of hydrocortisone at 200 mg/day was performed for 2 days, followed by maintenance therapy with prednisolone at 15 mg/day. Serum levels of cCa and iCa stabilized within 10.5-

Table. Laboratory Data on Admission.

WBC	7,690 / μ L	Glucose	124 mg/dL
Neutrocytes	81.7 %	Sodium	139.0 mEq/L
Lymphocytes	4.2 %	Potassium	4.04 mEq/L
Monocytes	11.3 %	Chloride	93.0 mEq/L
Eosinophils	2.5 %	Calcium	13.0 mg/dL
Basophils	0.3 %	Corrected calcium	14.2 mg/dL
Hemoglobin	12.1 g/dL	Ionized calcium	1.66 mmol/L
Platelets	26.5 \times 10 ⁴ / μ L	Phosphate	5.5 mg/dL
AST	14 IU/L	Magnesium	5.2 mg/dL
ALT	8 IU/L	intact PTH	17 pg/mL
ALP	407 IU/L	PTHrP	<1.0 pmol/L
γ -GTP	40 IU/L	1,25(OH) ₂ VitD	71.5 pg/mL
LDH	585 IU/L	25(OH)VitD	18.1 ng/mL
CK	13 U/L	ACTH	20.4 pg/dL
Total bilirubin	0.41 mg/dL	cortisol	15.7 μ g/dL
Total protein	6.8 g/dL	FT4	1.33 ng/dL
Albumin	2.8 g/dL	TSH	2.15 μ IU/mL
BUN	75.3 mg/dL	IGRA	negative
Creatinine	4.68 mg/dL	ACE	11.8 U/L
eGFR	10 mL/min/1.73m ²	free light chain κ/λ ratio	1.15
Uric acid	11.9 mg/dL	HTLV-1 Ab	negative
CRP	5.46 mg/dL	PSA	1.2 ng/mL
BNP	346.4 pg/mL	sIL-2R	6,260 U/mL
PT-INR	1.02	FECa	10.9 %
APTT	35.8 sec		
D-dimer	5.2 μ g/mL		

WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ -GTP: gamma-glutamyltransferase, LDH: lactate dehydrogenase, CK: creatine kinase, BUN: blood urea nitrogen, CRP: c-reactive protein, BNP: brain natriuretic peptide, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, intact PTH: intact parathormone, PTHrP: parathyroid hormone-related protein, 1,25(OH)₂VitD: 1-alpha, 25-dihydroxyvitamin D3, 25(OH)VitD: 25-hydroxyvitamin D3, ACTH: adrenocorticotrophic hormone, FT4: free thyroxine 4, TSH: thyroid stimulating hormone, IGRA: interferon-gamma release assays, ACE: angiotensin converting enzyme, HTLV-1 Ab: human T-cell leukemia virus type 1 antibody, PSA: prostate-specific antigen, sIL-2R: soluble interleukin-2 receptor, FECa: fractional excretion of calcium

11.5 mg/dL and 1.2-1.3 mmol/L, respectively. Consistent with these changes, the value for 1,25(OH)₂VitD decreased from 88.2 to 38.8 pg/mL before and 8 days after the administration of steroids, respectively (Fig. 4). These findings, along with the clinical course described above, supported the overproduction of 1,25(OH)₂VitD due to the activation of 1 α -hydroxylase in lymphoma lesions as the main mechanism responsible for the development of hypercalcemia.

Although the renal function slightly improved with the administration of saline and decrease in serum calcium levels, the eGFR did not recover over 25-35 mL/min/1.73 m². Zoledronic acid was not administered as continuous treatment in consideration of nephrotoxicity; therefore, denosumab at 120 mg/4 weeks was used as an alternative. Since the patient achieved a performance status of 4 and his serum calcium level stabilized with the denosumab and prednisolone treatments, we did not administer systemic chemotherapy for DLBCL, instead continuing supportive therapy.

Discussion

The clinical manifestations associated with hypercalcemia range from mild symptoms, such as fatigue or weakness, to severe symptoms, including acute renal insufficiency or coma, depending on the extent of hypercalcemia or disease progression. We herein report a case of impaired consciousness due to hypercalcemia associated with DLBCL. Impaired consciousness generally results from conditions such as metabolic disturbances, including uremia, hyper/hyponatremia, hypercalcemia, or drug overdose, infection, epilepsy, and intracranial disease. Laboratory tests on admission in the present case suggested hypercalcemia and renal failure as the causes of impaired consciousness. After the correction of dehydration and hypercalcemia, the conscious level improved to normal, whereas the renal function did not, indicating that hypercalcemia was the main cause of impaired consciousness. Regarding the cause of hypercalcemia, we initially suspected LOH because of the presence of osteolytic

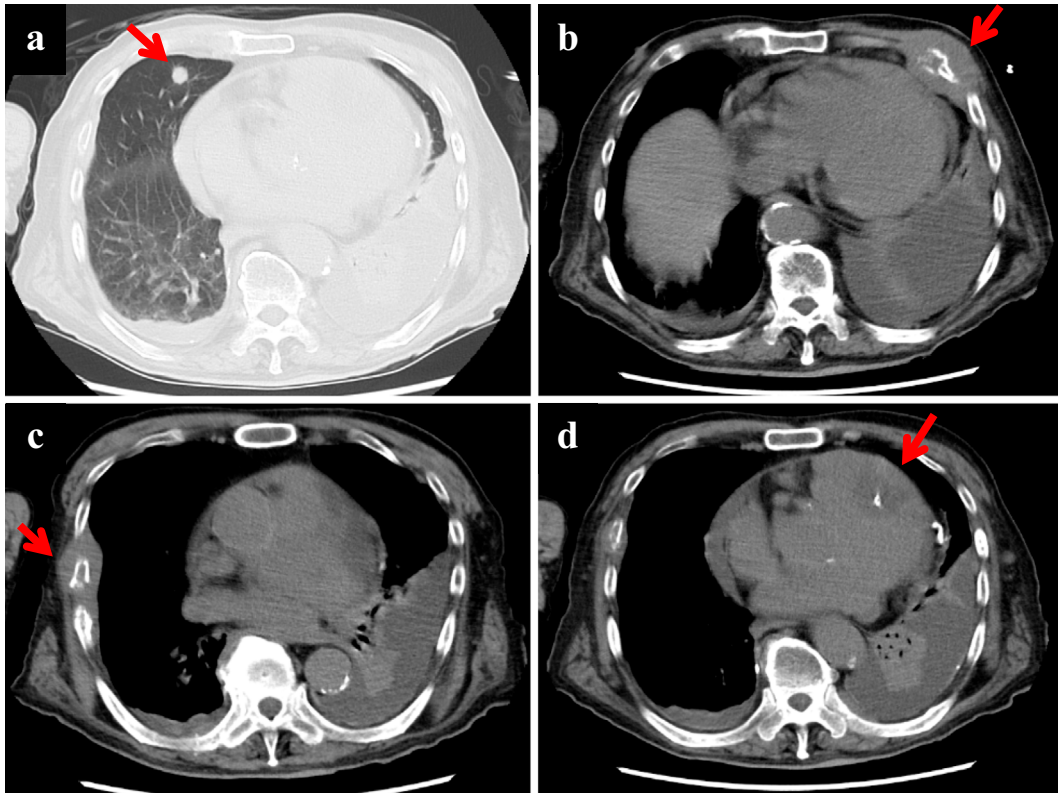


Figure 1. Computed tomography of the body on admission. A well-defined nodule was detected in the middle lobe of the right lung (a), masses with osteolytic changes were observed on the left 5th and right 6th and 7th ribs (b, c), and a soft tissue mass was found along the pericardium (d).

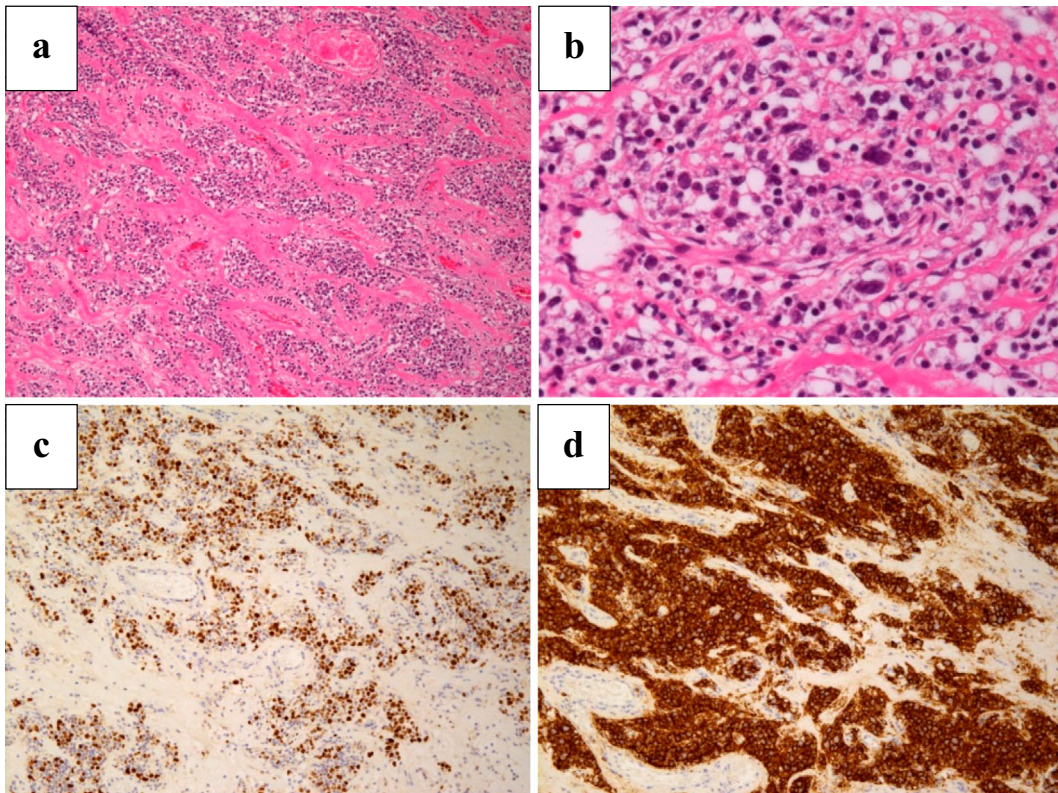


Figure 2. Pathological findings of the mass lesion on the left 5th rib. Hematoxylin and Eosin staining revealed diffuse atypical lymphocytes with nuclei of different sizes (a, b). Large lymphocytes were positive for CD20 (c) and Ki67 (d).

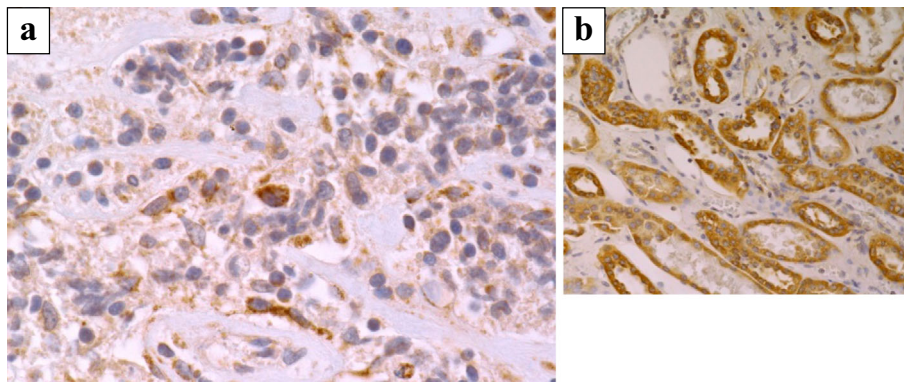


Figure 3. Immunostaining with the antibody against CYP27B1 (1α -hydroxylase) in the biopsy sample (a) and in normal proximal tubule tissue as the positive control (b).

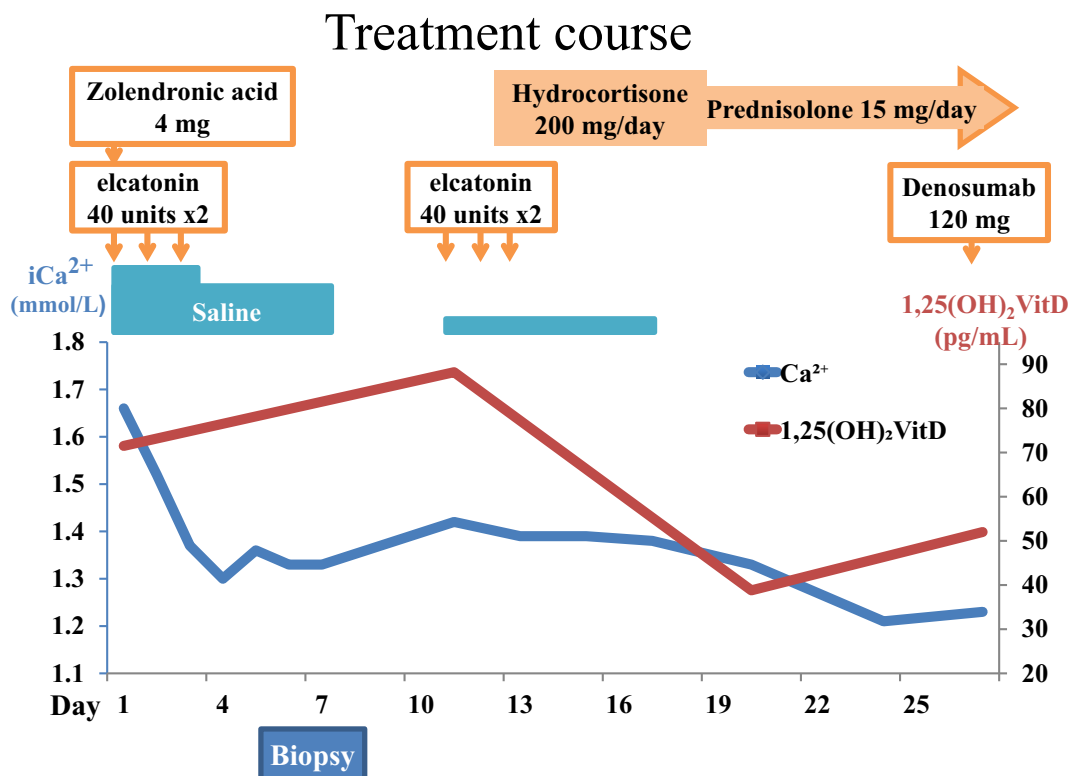


Figure 4. Clinical course of the patient.

changes in the left 5th and the right 6th and 7th ribs. However, the elevated serum level of $1,25(\text{OH})_2\text{VitD}$ despite hypercalcemia and end-stage kidney disease supported the overproduction of $1,25(\text{OH})_2\text{VitD}$ in the lesion. This was confirmed by the immunostaining of a biopsy sample with the antibody against CYP27B1, indicating that the ectopic expression of 1α -hydroxylase in lymphoma cells was the reason for hypercalcemia.

Fraser and Kodicek were the first to identify enzymatic activity for the synthesis of $1,25(\text{OH})_2\text{VitD}$ from $25(\text{OH})_2\text{VitD}$ in kidney homogenates in 1970 (15). However, $1,25(\text{OH})_2\text{VitD}$ production was subsequently discovered in anephric rodent models and humans, suggesting that extrarenal $1,25(\text{OH})_2\text{VitD}$ production may occur in organs other than the kidneys. Furthermore, extrarenal $1,25(\text{OH})_2\text{VitD}$

production was detected in the disease state of an anephric patient with sarcoidosis (16). The possible source was identified as activated pulmonary alveolar macrophages harvested from patients with sarcoidosis (17). The cloning of 1α -hydroxylase (CYP27B1) confirmed that the renal and extrarenal production of $1,25(\text{OH})_2\text{VitD}$ was mediated by the same enzyme, and it is expressed in other tissues as well, such as the skin, parathyroid glands, and placenta (18-20).

The extrarenal expression of CYP27B1 in macrophages is not limited to sarcoidosis; it has also been detected in other granuloma-forming diseases, such as tuberculosis, and malignancies, including malignant lymphoma. The extrarenal overexpression of CYP27B1 may also be observed in the immune system, such as in monocytes, dendritic cells, T cells, and B cells, as well in macrophages. It is important to

note that orthologs of the vitamin D receptor have been identified in single cell organisms, such as yeast or the vertebrae-lacking lamprey eel, suggesting that vitamin D plays roles in not only metabolic regulation but also other systems, including the immune system (18). Therefore, CYP27B1 may be ectopically expressed in immune cells or due to disorders of the immune system, such as lymphoma.

Although the renal and extrarenal activities of 1α -hydroxylase are achieved by the same gene product, the regulation of macrophage 1α -hydroxylase differs from that of renal 1α -hydroxylase. In the kidneys, renal 1α -hydroxylase is controlled by PTH and fibroblast growth factor 23 as well as by negative feedback between the synthesis of 25(OH)VitD and 1,25(OH)₂VitD. In contrast to renal 1α -hydroxylase, the expression of CYP27B1 in macrophages is not induced by PTH but is up-regulated by the presence of pro-inflammatory cytokines, such as interleukin 15 or interferon gamma, and is also stimulated by an increased level of 25(OH)VitD (19, 20). These findings suggest the mechanisms responsible for the development of hypercalcemia in granulomatous disorders in which activated macrophages constitutively express 1α -hydroxylase in the presence of elevated levels of calcium and 1,25(OH)₂VitD.

Hypercalcemia occurs in approximately 3.3-13% of non-Hodgkin's lymphomas and 1.6-5.4% of Hodgkin's lymphomas (1, 3, 9, 21). The incidence of hypercalcemia in high- and intermediate-grade non-Hodgkin's lymphomas may be as high as 30%, whereas it is very uncommon in the low-grade state, occurring in only 1% to 2% of cases. Although limited information is currently available, 30-40% of cases of hypercalcemia in non-Hodgkin's lymphoma appeared to be associated with increased levels of 1,25(OH)₂VitD. However, the cellular source of 1,25(OH)₂VitD in lymphoma remains unclear. The conversion of 25(OH)VitD to 1,25(OH)₂VitD *in vitro* using a lymph node homogenate strongly supported production in the lesions of lymphoma. In 2003, Hewison et al. reported that macrophages adjacent to lymphoma cells stained positively for 1α -hydroxylase, indicating that the local activation of vitamin D is mediated by macrophages at the tumor interface (12). In contrast, another group suggested that lymphoma cells themselves were the site for the excessive synthesis of 1,25(OH)₂VitD (13, 14). In the present case, the immunostaining of lymphoma tissue with the 1α -hydroxylase (CYP27B1) antibody clearly showed the ectopic expression of 1α -hydroxylase in lymphoma cells. Since 1α -hydroxylase-expressing cells were morphologically defined as lymphoma cells, double staining with the antibody against anti-CD20 may be required to confirm the expression of 1α -hydroxylase in lymphoma cells but not in the macrophages adjacent to lymphoma cells.

The management of hypercalcemia includes hydration, elcatonin, bisphosphonates, denosumab, and in some patients, corticosteroids and cinacalcet. Corticosteroids are effective for not only the treatment of lymphoma but also 1,25(OH)₂VitD-mediated hypercalcemia. Corticosteroids inhibit the 1α -hydroxylase-mediated conversion of 25(OH)VitD into

$1,25(OH)_2$ VitD, thereby reducing intestinal calcium absorption. Treatment generally consists of intravenous hydrocortisone at 200-400 mg/day for 3-5 days followed by oral prednisone at 10-20 mg/day for an additional 7 days (5, 22). In the present case, since zoledronic acid exerted limited inhibitory effects on hypercalcemia, the continuous intravenous infusion of hydrocortisone at 200 mg/day was performed for 2 days, followed by maintenance therapy with prednisolone at 15 mg/day to suppress 1α -hydroxylase.

In conclusion, we encountered a case of hypercalcemia induced by the overproduction of 1,25(OH)₂VitD in DLBCL. Immunostaining with the anti-CYP27B1 antibody was useful for identifying the ectopic expression of 1α -hydroxylase in lesions and facilitated the selection of corticosteroids as the treatment to control hypercalcemia in malignancy.

The authors state that they have no Conflict of Interest (COI).

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