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Case report

Anaplastic large cell lymphoma, with $1,25(OH)_2D_3$-mediated hypercalcemia: A case report

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Hypercalcemia due to malignant tumors including malignant lymphomas is relatively common. Among cancer patients with hypercalcemia, humoral hypercalcemia of malignancy is the most common and accounts for about 80% of all cases with hypercalcemia. 1,25-dihydroxyvitamin D_3($1,25(OH)_2D_3$)-mediated hypercalcemia is relatively rare. Although malignant lymphoma has been also reported to cause $1,25(OH)_2D_3$-mediated hypercalcemia, it is not known whether there is any association between $1,25(OH)_2D_3$-mediated hypercalcemia and any specific histological type of malignant lymphoma. We herein report a case of an anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK) -negative with $1,25(OH)_2D_3$-mediated hypercalcemia, which has never been previously reported. An 80-year-old Japanese man was admitted to our department due to acute exacerbation of hypercalcemia. He was diagnosed with ALCL, ALK-negative. Serum $1,25(OH)_2D_3$ level was high and seemed to be associated with the lymphoma because the serum calcium and $1,25(OH)_2D_3$ levels improved in response to chemotherapy. Histological findings showed that many CD68 positive macrophages were observed in the microenvironment of tumor cells. Lymphoma cells or tumor microenvironmental cells may produce $1,25(OH)_2D_3$ because several previous reports showed the source of $1,25(OH)_2D_3$ can be either lymphoma or tumor microenvironmental cells. Moreover, because $1,25(OH)_2D_3$-mediated hypercalcemia has been reported regardless of the specific histological type of lymphoma, tumor microenvironmental cells may be involved in this condition. However, we could not identify the source of $1,25(OH)_2D_3$ in this case. The association between $1,25(OH)_2D_3$ production and prognosis in malignant lymphomas is yet unknown; further studies are needed to elucidate the clinical characteristics of malignant lymphoma with $1,25(OH)_2D_3$-mediated hypercalcemia.

Keywords: 1,25-dihydroxyvitamin D_3, hypercalcemia, anaplastic large cell lymphoma

INTRODUCTION

Hypercalcemia due to malignancy is relatively common and occurs in approximately 20-30 percent patients with cancer.[1] The pathogenesis of hypercalcemia due to malignancy is classified into three categories: humoral hypercalcemia of malignancy (HHM) due to parathyroid hormone related protein (PTHrP) secreted by tumor, local osteolytic hypercalcemia (LOH) caused by bone invasion, and 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$)-mediated hypercalcemia.[2,3] Among these categories, HHM is the most common, accounting for about 80% of all cases with hypercalcemia.[4]

Although multiple myeloma and adult T-cell leukemia/lymphoma are common hematological malignancies that cause hypercalcemia, malignant lymphoma can also be a cause of hypercalcemia.[5] In a previous report, approximately 5% patients with Hodgkin lymphomas (HL) and 13% patients with non-Hodgkin lymphomas (NHL) showed hypercalcemia.[6] $1,25(OH)_2D_3$-mediated hypercalcemia was reported to be the most frequent in HL cases; almost all cases of hypercalcemia due to HL showed high serum $1,25(OH)_2D_3$ level.[6] On the other hand, HHM has been frequently observed in NHL cases;[7] one study observed high serum $1,25(OH)_2D_3$ levels only in one third of NHL cases with hypercalcemia.[6] In addition, the association between specific histological type of NHL and $1,25(OH)_2D_3$ has not been confirmed, and cases of anaplastic large cell lymphoma (ALCL) with $1,25(OH)_2D_3$-mediated hypercalcemia has not been reported.

We herein report a case of hypercalcemia due to ALCL,

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ALK-negative, which seems to be producing $1,25(OH)_2D_3$.

CASE REPORT

The patient was an 80-year-old Japanese man with a past medical history of hypertension, dyslipidemia, and acute myocardial infarction (percutaneous coronary intervention was performed 4 years ago). He presented with right cervical lymphadenopathy and cervical pain 1 month before admission and visited a local clinic. He was administered cefcapene pivoxil and prednisolone; however, the symptoms did not improve. Three days before admission, he was referred to our hospital; his blood test showed the following results: corrected serum calcium level, 13.0 mg/dL; C-reactive protein (CRP) level, 6.87 mg/dL; and lactate dehydrogenase (LDH) level, 1453 IU/L. Serum calcium level increased rapidly to 14.0 mg/dL in 3 days and he was hospitalized urgently.

On admission, his consciousness was lucid, body temperature was 36.9°C, blood pressure was 116/77 mmHg, pulse rate was 66/min, and oxygen saturation was 94% on room air. Eye examination showed no anemia or jaundice. Head and neck examination revealed right mandibular and cervical lymphadenopathies, sized 10-20 mm, with tenderness. No other palpable superficial lymph nodes were found. Breath and heart sounds were normal. Abdominal examination showed no hepatosplenomegaly. Pitting edema was confirmed in the lower extremities. His general condition was poor, and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was 4. B symptoms (fever, night sweats, and weight loss) were not observed.

We investigated the cause of hypercalcemia after admission. In the laboratory data (Table 1), blood examination revealed that $1,25(OH)_2D_3$ level was high, 25-hydroxyvitamin D_3 level was normal, intact parathyroid hormone level was low, PTHrP was not detected, calcitonin level was normal, and angiotensin-converting enzyme level was low. Serum monoclonal protein and urine Bence-Jones protein were not detected. Human T-cell Leukemia Virus type 1 antibody and QuantiFERON® tests were negative. Computed tomography (CT) showed lymphadenopathies in the right neck, right supraclavicular, superior mediastinal, and right axillary nodes, and under the tracheal branch and pancreas head. Evident neoplastic bone lesions were not found (Figure 1).

On the 1st hospital day, we started massive saline infusion, furosemide, and calcitonin derivative to improve hypercalcemia. Cervical lymph node biopsy was performed on the 5th hospital day. Hematoxylin-eosin staining showed large abnormal lymphocytes in the lymph node. Immunohistochemistry revealed that tumor cells were CD3 negative, CD20 negative, CD4 positive, CD8 negative, CD30 positive, ALK negative, TIA-1 positive, PAX5 negative, CD68 negative, AE1/AE3 negative, and Granzyme B negative. In addition, CD68-positive cells, which were considered to be macrophage- or monocyte-like cells, were observed in the microenvironment of tumor cells (Figure 2). Chromosomal abnormalities could not be detected from G-banding because enough metaphase cells were not obtained. Bone marrow biopsy showed no tumor invasion. Based on the above findings, he was diagnosed with ALCL, ALK-negative (Clinical stage: IIIA, International Prognostic Index (IPI): high-risk).

Although the most common chemotherapy regimen for ALCL, ALK-negative is CHOP therapy (cyclophosphamide,

Table 1. Laboratory data on admission

RBC	476×104	/μL	γ-GTP	45	IU/L	IgG	1036	mg/dL
Hb	14.4	g/dL	ALP	275	IU/L	IgA	155	mg/dL
Hct	43.3	%	ChE	189	mg/dL	IgM	142	mg/dL
WBC	5680	/μL	T-Bil	0.6	mg/dL	aPTT	33.0	sec
Neut	80.8	%	BUN	26	mg/dL	PT-INR	1.04	
Lym	8.8	%	Cre	1.1	mg/dL	HTLV-1 antibody	(-)	
Eos	1.6	%	Na	138	mEq/L	QuantiFERON test	(-)	
Bas	0.7	%	K	4.6	mEq/L	Serum M-protein	(-)	
Mon	8.1	%	Cl	99	mEq/L	Urine BJP	(-)	
Plt	21.6×10^4	/μL	Ca	14	mg/dL	$1,25(OH)_2D_3$	227 (20-60)	pg/mL
TP	7.1	g/dL	I-P	4.6	mg/dL	$25(OH)D_3$	16.1 (≤20)	ng/mL
Alb	3.2	g/dL	CRP	10.16	mg/dL	intact PTH	<3.00 (15-65)	pg/mL
AST	217	IU/L	sIL-2R	8685	IU/mL	PTHrP	<1.00 (<1.1)	pmol/L
ALT	40	IU/L	Ferritin	690	ng/mL	Calcitonin	2.0 (≤5.15)	pg/mL
LDH	1549	IU/L	β2MG	2.0	mg/L	ACE	2.3 (6.6-21.4)	IU/L

RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell, Neut: neutrophil, Lym: lymphocyte, Eos: eosinophil, Bas: basophil, Mon: monocyte, Plt: platelet, TP: total protein, Alb: albumin, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, ChE: cholinesterase, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, I-P: inorganic phosphate, CRP: C-reactive protein, sIL-2R: soluble interleukin-2 receptor, β2MG: β2-microglobulin, APTT: activated partial thromboplastin time, PT-INR: prothrombin time-international normalized ratio, HTLV-1: human T-lymphotropic virus type 1, M-protein: monoclonal protein, BJP: Bence-Jones protein, $1,25(OH)_2D_3$: 1,25-dihydroxyvitamin D_3, $25(OH)D_3$: 25-hydroxyvitamin D_3, PTH: parathyroid hormone, PTHrP: parathyroid hormone related protein, ACE: angiotensin-converting enzyme

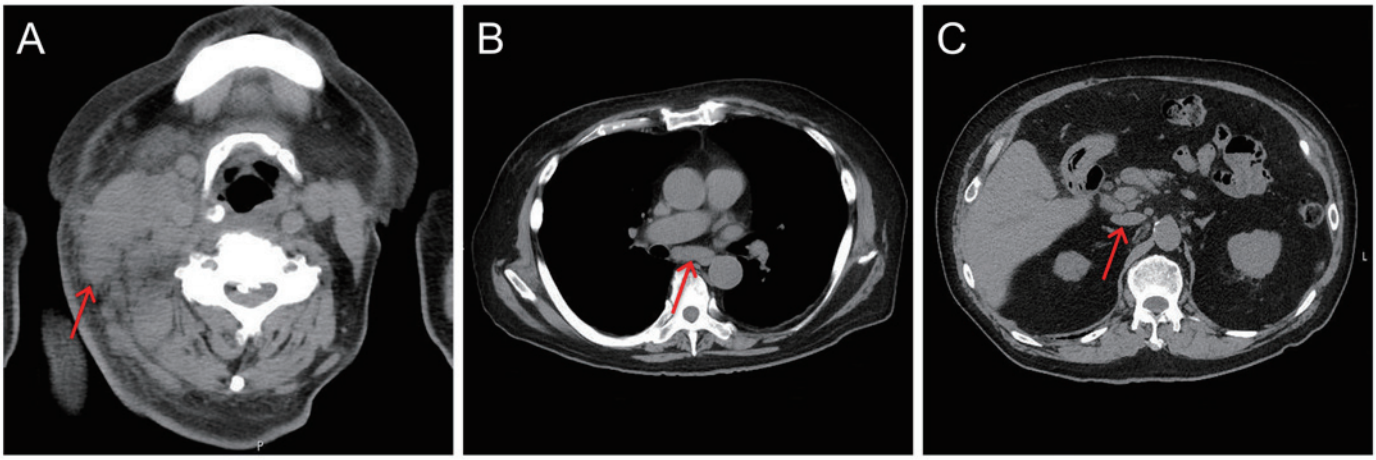

Fig. 1. Systemic computed tomography (CT) scan images on admission.
Systemic CT scan showed lymphadenopathies at (***A***) right neck, right supraclavicular, superior mediastinal, and right axillary lymph nodes; (***B***) under tracheal branch; and (***C***) under tracheal branch. Evident neoplastic bone lesions were not found.

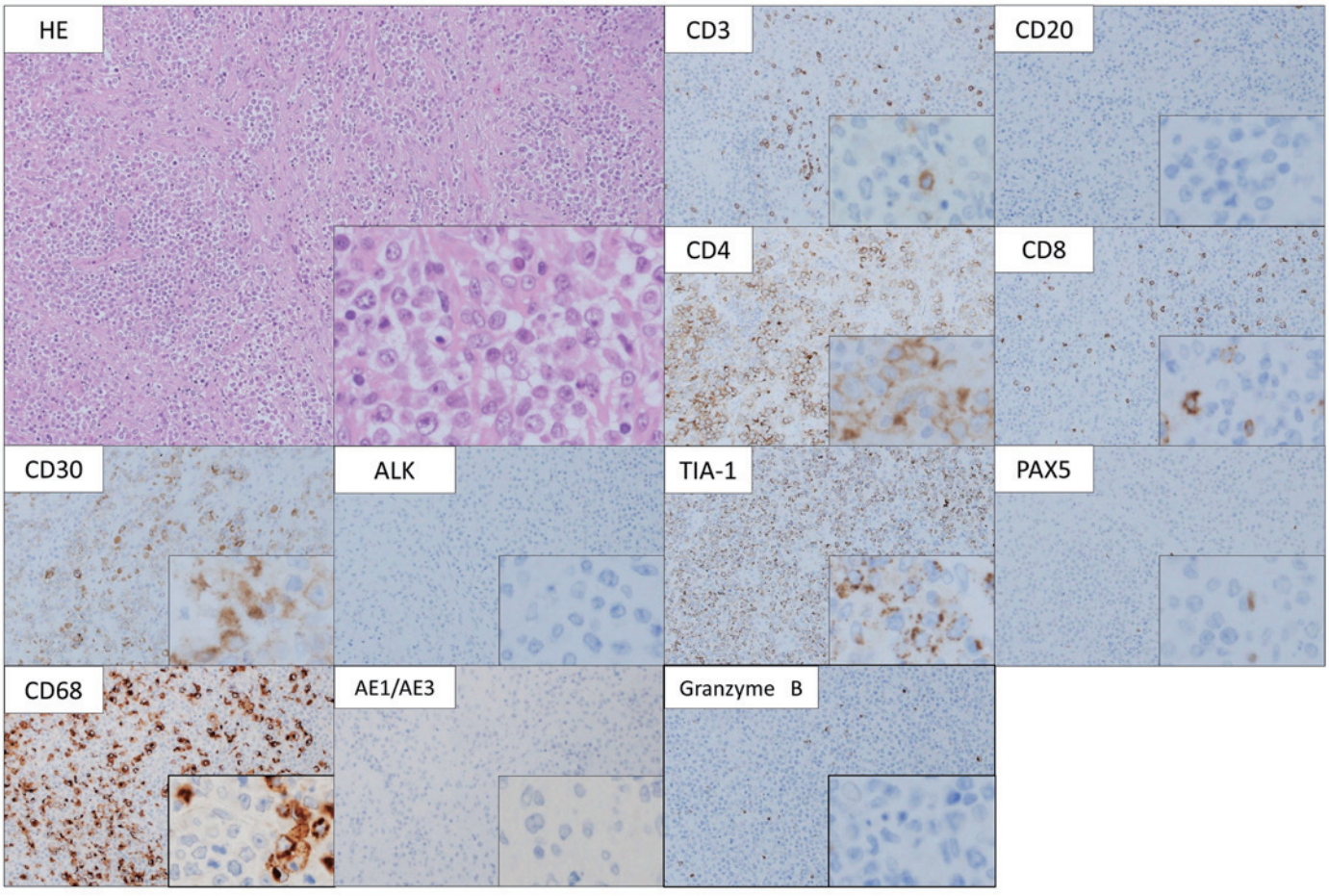

Fig. 2. Pathological images of cervical lymph node biopsy on the 5th hospital day.
Hematoxylin-eosin (HE) staining showed large atypical lymphocytes growing in the tissue. Immunostaining revealed that tumor cells were CD3(-), CD20(-), CD4(+), CD8(-), CD30(+), ALK(-), TIA-1(+), PAX5(-), CD68(-), AE1/AE3(-) and Granzyme B(-). CD68-positive histiocytes were observed around the tumor cells.

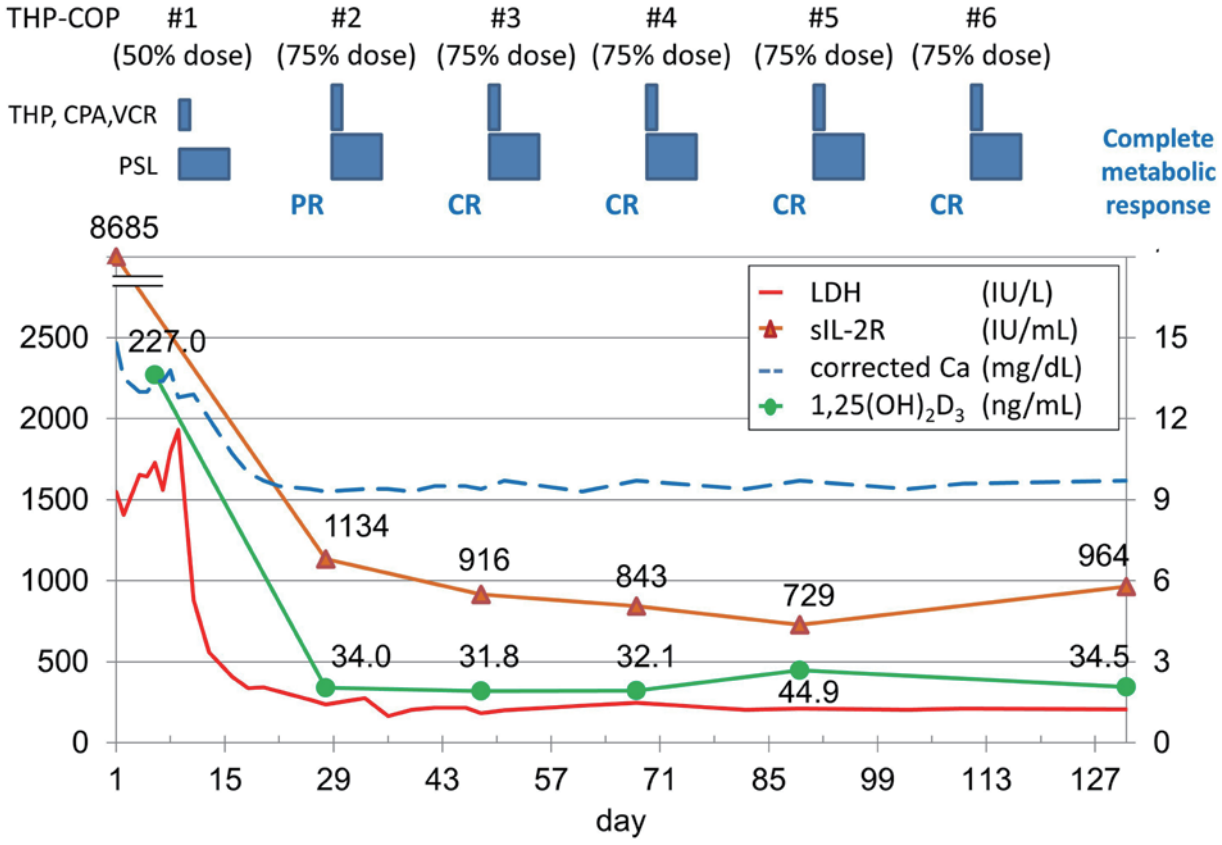

Fig. 3. Transition of lactate dehydrogenase (LDH), soluble interleukin-2 receptor (sIL2-R), corrected serum calcium (corrected Ca), and 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$).
Corrected Ca and $1,25(OH)_2D_3$ are improved in parallel with LDH and sIL2-R. Day 1 is the date of hospitalization. THP: therarubicin, CPA: cyclophosphamide, VCR: vincristine, PSL: prednisolone, PA: partial response, CR: complete response.

doxorubicin, vincristine, and prednisolone), we selected THP-COP (therarubicin, cyclophosphamide, vincristine, and prednisolone) because the patient had a past medical history of acute myocardial infarction. On the 8th hospital day, ECOG-PS was noted to be very poor; therefore, we started 50% dose of THP-COP. At the end of the 1st cycle of THP-COP, CT showed 70% tumor reduction and we confirmed partial response (PR). His general condition was improving, and his corrected serum calcium and $1,25(OH)_2D_3$ returned to the normal range, along with decreases in LDH and soluble interleukin-2 receptor (sIL2-R) levels (Figure 3). On the 28th hospital day, we started the 2nd cycle with a 75% dose of THP-COP. Complete response (CR) with 90% tumor reduction was confirmed by CT at the end of the cycle. On the 48th hospital day, we started the 3rd cycle with 75% dose of THP-COP. On the 51st hospital day, he was discharged because he was able to receive outpatient chemotherapy. His corrected serum calcium level was 9.7 mg/dL and $1,25(OH)_2D_3$ level was 31.8 ng/dL. Until the 6th and final cycle of THP-COP, CR was maintained, and corrected serum calcium and $1,25(OH)_2D_3$ levels did not increase again. We confirmed complete metabolic response by ^{18}F-fluorodeoxy glucose positron emission tomography at the end of the 6th cycle (Figure 4). At the latest follow-up 10 months, he has maintained CR.

DISCUSSION

This case showed $1,25(OH)_2D_3$-mediated hypercalcemia because serum $1,25(OH)_2D_3$ level was high, and multiple myeloma, hyperparathyroidism, medullary thyroid cancer, LOH, or granulomatous disease such as sarcoidosis or tuberculosis were not considered. Response to the treatment for ALCL, ALK-negative (tumor reduction and decreases of LDH and sIL2-R) was correlated to normalizations of corrected serum calcium and $1,25(OH)_2D_3$ levels, and they had not increase again in the remission phase (Figure 3). Moreover, as in the previous reports of malignant lymphomas with $1,25(OH)_2D_3$-mediated hypercalcemia,[8-18] responses to treatment for malignant lymphomas were correlated to normalizations of corrected serum calcium and $1,25(OH)_2D_3$ levels (Table 2).[8,11,12,15-17] From the above reports, we suspected that ALCL cells were associated with $1,25(OH)_2D_3$ production in this case.

25-hydroxyvitamin D_3-1α-hydroxylase (CYP27B1) have been reported to be associated with $1,25(OH)_2D_3$ production.[19,20] CYP27B1 acts primarily on the renal proximal tubes; however, it is also expressed in many extra-renal tissues including macrophages.[19] Expression of CYP27B1 has been also reported in various malignant tumors such as colon cancer, breast cancer, and prostate cancer.[19] In these cancers

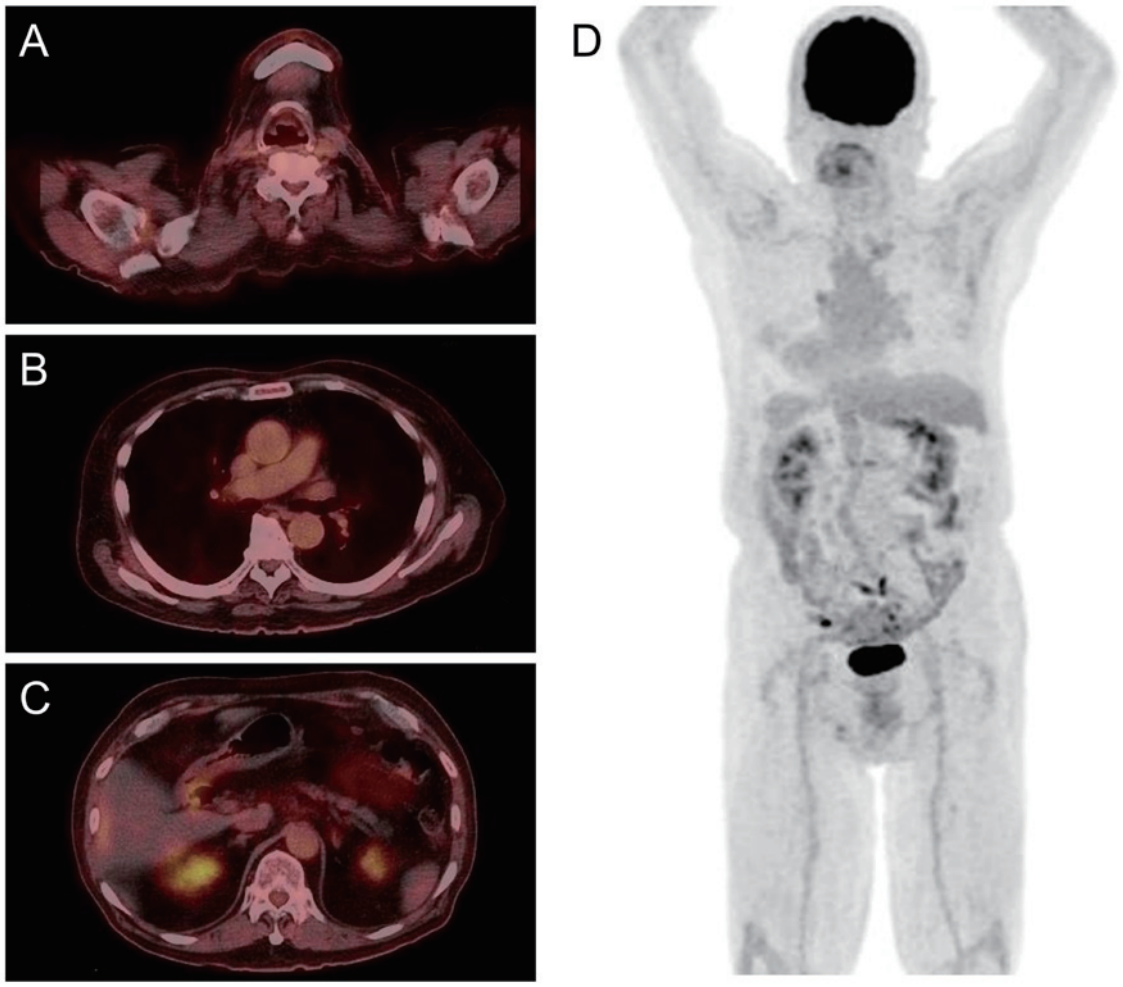

Fig. 4. ^{18}F-fluorodeoxy glucose positron emission tomography (FDG-PET) images after 6th cycle of THP-COP therapy.
FDG-PET showed that lymphadenopathy at (***A***) right neck, right supraclavicular, superior mediastinal, and right axillary lymph nodes; (***B***) subcarinal lymph nodes; and (***C***) pancreas head had disappeared. No significant accumulations of FDG were observed (***D***). We confirmed complete metabolic response.

with hypercalcemia, the regulation of CYP27B1 by $1,25(OH)_2D_3$ within a negative feedback loop is believed to be lost in malignant cells because of the gene mutation.[19] On the other hand, in granulomatous diseases such as sarcoidosis and tuberculosis, hypercalcemia is induced by the hyperactivity of CYP27B1 in the macrophages in granuloma. This is associated with cytokines such as interferon-γ, tumor necrosis factor-α and interleukin-1,2,15.[20-22] In this case, inflammatory reaction involving the elevation of CRP level was observed. Therefore, it can be concluded that macrophages and cytokines might be associated with hypercalcemia.

In previous reports of malignant lymphomas with $1,25(OH)_2D_3$ production (Table 2), two cases expressed CYP27B1. One was expressed in lymphoma cells[8] and the other in the macrophages around lymphoma cells.[13] As mentioned above, there are two theories as to the pathogenesis of $1,25(OH)_2D_3$ production in lymphoma: CYP27B1 mutation in tumor cells, and CYP27B1 hyperactivity in macrophages around tumor cells; these cases suggest that both theories are possible. The letter theory is possibly associated with cytokines produced by the lymphoma. It is currently unknown whether it is the tumor cells or the tumor microenvironment that produce $1,25(OH)_2D_3$. In our case, ALCL cells or tumor microenvironment were assumed to produce $1,25(OH)_2D_3$ because histiocytes and macrophages were confirmed in the tumor microenvironmental cells (Figure 2). However, we could not identify $1,25(OH)_2D_3$ production in either lymphoma or tumor microenvironmental cells.

Though we could not provide any evidence of a direct relationship between lymphoma and $1,25(OH)_2D_3$ production, we assumed that the lymphoma was associated with $1,25(OH)_2D_3$ production in some way because treatment response showed correlation with normalization of $1,25(OH)_2D_3$ levels. The tumor itself, like other malignancies or macrophage-like granulomatous diseases seems to produce $1,25(OH)_2D_3$ because both have been reported previously in malignant lymphoma.[8,13]

In conclusion, although 1,25-dihydroxyvitamin D_3-producing cells in ALCL, ALK-negative could not be directly identified, we demonstrated a case of hypercalcemia

Table 2. Previous reports of malignant lymphoma with $1,25(OH)_2D_3$-mediated hypercalcemia

year	Previous reports	Onset age	Sex	Classification of the lymphoma	Primary site	Treatment	1,25(OH)2D3 (pg/mL)		Serum calcium (mg/dL)		Treatment response or outcome
							Initial	Post Tx	Initial	Post Tx	
2018	Nakayama S, *et al.*[8]	78	M	DLBCL (non-GCB)	Nasal cavity	R-CHOP	81.7	59.2	10.4	8.8	CR
2018	Chams S, *et al.*[9]	83	M	AITL	NA	Untreated	85.4	NA	11.7	NA	Death (PD)
2016	Abaroa-Salvatierra A, *et al.*[10]	81	M	DLBCL	Adrenal	R-CVP	90	NA	14	NA	Death (PD)
2016	Mir SA, *et al.*[11]	65	M	DLBCL	Adrenal	R-CHOP	213.4	NA	14.2	8.9	CR
2006	Gupta R, *et al.*[12]	79	F	Hodgkin lymphoma	Axillary LN	Chemotherapy	248	Normal	21.0	10.7	CR
2003	Hewison M, *et al.*[13]	75	M	Large intermediate grade BCL	Spleen	Splenectomy	140	20*	12.7	Normal	NA
1999	Adams JS, *et al.*[14]	29	M	BCL (small non-cleaved)	NA	Hydroxychloroquine†	96*	70*	11.9*	11.5*	NA
		77	F	BCL (small non-cleaved)	NA	Hydroxychloroquine†	94*	70*	11.3*	10.8*	NA
		74	F	BCL (small non-cleaved)	NA	CHOP	125*	40*	14.3*	9.4*	NA
		67	F	BCL (small non-cleaved)	NA	CHOP	86*	14*	13.1*	10.0*	NA
1998	Moore JJ, *et al.*[15]	48	M	DLBCL (T-cell rich)	Para-vertebral	CHOP, BMT	206	Decreased	15.2	Decreased	Death (BMT related)
1991	Scheinman SJ, *et al.*[16]	58	M	angiocentric lymphoma	NA	CHOP	170	Normal	15.1	Normal	CR
1988	Mercier RJ, *et al.*[17]	40	M	Hodgkin lymphoma	NA	BCVPP	248	21.6	14	Normal	CR
1986	Schaefer K, *et al.*[18]	74	F	Hodgkin lymphoma	NA	Prednisolone	105*	40*	14.2	8.5*	NA

DLBCL: diffuse large B-cell lymphoma; GCB: germinal center B-cell-like; AITL: angioimmunoblastic T-cell lymphoma; BCL: B-cell lymphoma; NA: not available; LN: lymph node; R: rituximab; CHOP: cyclophosphamide(CPA), doxorubicin, vincristine(VCR), prednisolone(PSL); CVP: CPA, VCR, PSL; BMT: bone marrow transplantation; BCVPP: carmustine, CPA, vinblastine, procarbazine, PSL; Tx: treatment; †: hydroxychloroquine is reported to reduce serum calcium level in sarcoidosis; *: read from figure (value is not stated); CR: complete response; CYP27B1: 25-hydroxyvitamin D3-1α-hydroxylase.

due to the production $1,25(OH)_2D_3$ by ALCL, ALK-negative. To our knowledge, this is the first report of ALCL with $1,25(OH)_2D_3$-mediated hypercalcemia. Further studies and more cases will be needed to investigate the exact pathogenesis of $1,25(OH)_2D_3$ production.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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