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Case Report

The Effectiveness of Combined Medical Therapy and Hemodialysis for Hypercalcemia in Anaplastic Lymphoma Kinase-negative Anaplastic Large Cell Lymphoma

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Abstract: A 71-year-old man with a right lower abdominal quadrant epithelial tumor developed gradually worsening lumbago and dysbasia. He became comatose and was admitted to our hospital. He had swelling of the left axillary lymph nodes and necrosis of the 4.0-cm diameter abdominal tumor, which infiltrated the subcutaneous tissues. He was hypercalcemic (16.7 mg / dl), and had elevated levels of soluble interleukin-2 receptor (24,090 U / ml) and parathyroid hormone-related protein (5.4 pmol / l). Computerized tomography (CT) showed left axillary lymphadenopathy, splenomegaly, and a right abdominal-wall mass that was described as anaplastic large cell lymphoma upon pathology. Brain radiography and CT revealed multiple lesions infiltrating the cranium. Magnetic resonance imaging showed diffuse low signal intensity throughout the vertebral spine. The patient was diagnosed with anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma with hypercalcemia. Fluid replacement and drug therapies including calcitonin had no effect on the hypercalcemia or the coma. The patient's serum calcium concentration decreased after hemodialysis (calcium dialysate concentration, 5 mg / dl) and subsequent zoledronic acid hydrate therapy. His consciousness improved by the fifth day of treatment. This rare case of hypercalcemia in ALK-negative anaplastic large cell lymphoma improved with combined medical and hemodialysis therapy.

Key words: hypercalcemia of malignancy, coma, hemodialysis, anaplastic large cell lymphoma, ALK negative

Introduction

There are many cerebral and systemic diseases capable of causing coma. The cerebral causes include cerebrovascular disease, brain tumor, brain damage, encephalitis, and meningitis, whereas the systemic causes include hypothermia, hypoxemia, sepsis, electrolyte abnormalities, glucose metabolism disorders, endocrine diseases, and drug intoxication. Hypercalcemia is an electrolyte

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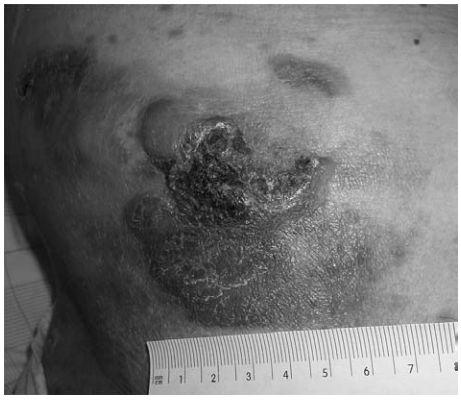

Fig. 1. The epithelial tumor was in the right lower abdominal quadrant : the tumor was 4.0 cm in diameter, with necrosis and subcutaneous infiltration.

abnormality that induces coma by interfering with nerve impulse transmission. If medical treatment is delayed or the hypercalcemia is prolonged, then the condition can become life-threatening. It is crucial to rapidly and markedly decrease the patient's serum calcium level. If the usual medical treatments fail to produce a rapid effect, then combining medical therapy with hemodialysis is the treatment of choice[1].

Hypercalcemia is common in patients with malignancy and occurs in approximately 20 ～ 30% of cases[2]. The primarily cause of hypercalcemia is increased bone resorption with the subsequent release of calcium. There have been no previous reports of hypercalcemia occurring in patients with anaplastic large cell lymphoma (ALCL). Here, we report a patient with the rare combination of hypercalcemia and anaplastic lymphoma kinase (ALK)-negative ALCL. This patient recovered well from hypercalcemia-induced coma following combined medical and hemodialysis therapy.

Case Report

A 71-year-old Japanese man was diagnosed with an epithelial tumor in the right lower abdominal quadrant in May 2011. He developed gradually worsening lumbago and dysbasia in April 2012, and in May 2012 he became comatose (Glasgow Coma Scale score, 10 points) and was admitted to our hospital. His past history was relevant for hypertension because his family history revealed gastric cancer in his brother and pancreatic cancer in his sister. His blood pressure at admission was 118 / 60 mm Hg, his body temperature was 36.8℃, and his pulse rate was 66 beats per minute. His conjunctiva were neither pale nor jaundiced. His breath sounds and heartbeat were normal. The left axillary lymph nodes were swollen, but no other lymphadenopathy was detected. A 4.0-cm diameter epithelial tumor with necrosis and the subcutaneous infiltration was identified in the right lower abdominal quadrant (Fig. 1). The patient's muscle strength was level 4 on the Manual Muscle Test scale and there

Table 1. Laboratory findings on admission

Blood cell count		Serological test	
WBC / μL	23×10^2	IgG mg / dL	1752
RBC / μL	532×10^4	IgA mg / dL	416
Hb g / dL	17.0	IgM mg / dL	233
Plt / μL	10.4×10^4	whole PTH pmol / L	< 6
		PTHrP pmol / L	5.4
Blood chemistry		$1\text{-}25(OH)_2VitD_3$ pg / mL	25
TP g / dL	7.4	PSA ng / mL	0.167
Alb g / dL	3.1	CEA ng / mL	1.5
UN mg / dL	38	SCC ng / mL	0.2
Cr mg / dL	0.9	SLX U / mL	31.1
UA mg / dL	18.4	NSE ng / mL	122.5
Na mEq / L	142	cytokeratin 19 ng / mL	1.8
K mEq / L	3.8	AFP ng / mL	3
Cl mEq / L	90	sIL-2R U / mL	24090
Ca mg / dL	16.7	M protein	−
P mg / dL	3.4	Bence-Jones ptotein	−
AST U / L	82	HTLV-1 antibody	−
ALT U / L	62		
γ-GTP U / L	70	Urinalysis	
ALP U / L	275	Protein	−
LDH U / L	369	Occut blood	1 +
Glu mg / dL	131		
hsCRP mg / dL	1.8		

WBC = white blood cell count ; RBC = red blood cell ; Hb = hemoglobin ; Plt = blood platelet ; TP = total protein ; Alb = albumin ; UN = blood urea nitrogen ; Cr = creatinine ; UA = uric acid ; Na = sodium ; K = potassium ; Cl = chloride ; Ca = calcium ; iP = inorganic phosphorus ; AST = aspartate aminotransferase ; ALT = alanine aminotransferase ; γ-GTP = γ-glutamyltranspeptidase ; ALP = alkaline phosphatase ; LDH = lactate dehydrogenase ; Glu = glucose ; hsCRP = high sensitivity C-reactive protein ; IgG = immunoglobulin G ; IgA = immunoglobulin A ; IgM = immunoglobulin M ; whole PTH = whole parathyroid hormone ; PTHrP = parathyroid hormone-related protein ; $1\text{-}25(OH)_2VitD_3$ = 1,25-dihydroxyvitamin D_3 ; PSA = prostate-specific antigen ; CEA = carcinoembryonic antigen ; SCC = squamous cell carcinoma antigen ; SLX = sialyl Lewis X-i antigen ; NSE = neuron-specific enolase ; AFP = alpha-fetoprotein ; sIL-2R = soluble interleukin-2 receptor ; M protein = monoclonal protein ; ATLA = adult T-cell leukemia-associated antigen

was no paralysis of the limbs. The laboratory data are shown in Table 1 and the notable findings were : hypercalcemia (16.7 mg / dl), elevated levels of soluble interleukin-2 receptor (sIL-2R) (24,090 U / ml) and parathyroid hormone-related protein (PTHrP) (5.4 pmol / l), whole parathyroid hormone and active vitamin D levels were not elevated. The patient had thrombocytopenia and the results for immunoelectrophoresis analysis were negative for

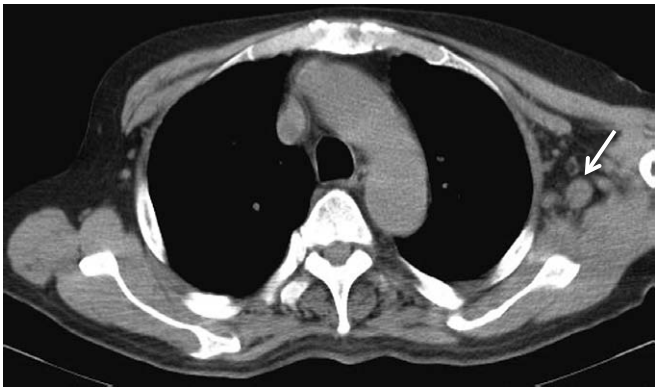

Fig. 2. Chest computed tomography (CT) shows left axillary lymphadenopathy is indicated by the arrow.

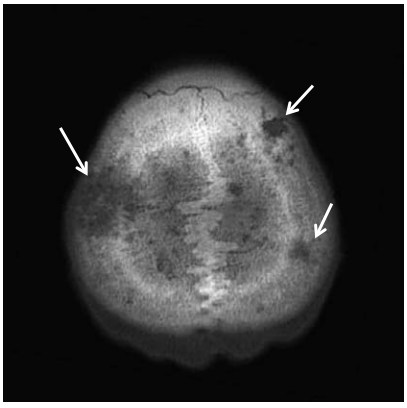

Fig. 3. Brain CT (bone window) shows multiple infiltrating lesions in the cranial bones are indicated by the arrows.

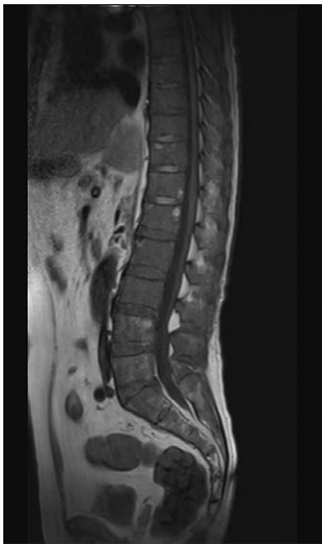

Fig. 4. T1-weighted magnetic resonance imaging shows diffuse low signal intensity throughout the vertebral spine.

monoclonal immunoglobulin and Bence-Jones protein in blood and urine. The test for anti-adult T-cell leukemia-associated antigen antibody yielded a negative result. Plain chest radiography did not show hilar lymphadenopathy or any other abnormalities. An electrocardiogram showed normal sinus rhythm without a prolonged Q-T interval (QTc interval, 436 ms). Chest computerized tomography (CT) showed left axillary lymphadenopathy (Fig. 2). Abdominal CT revealed splenomegaly and a right abdominal wall mass of slightly higher density than muscle (image not shown). Brain radiography and brain CT for bone condition revealed multiple infiltrating lesions in the cranial bones (Fig. 3). T1-weighted magnetic resonance imaging showed diffuse low signal intensity throughout the vertebral spine (Fig. 4). Based on these findings, we diagnosed clinically malignant lymphoma with hypercalcemia.

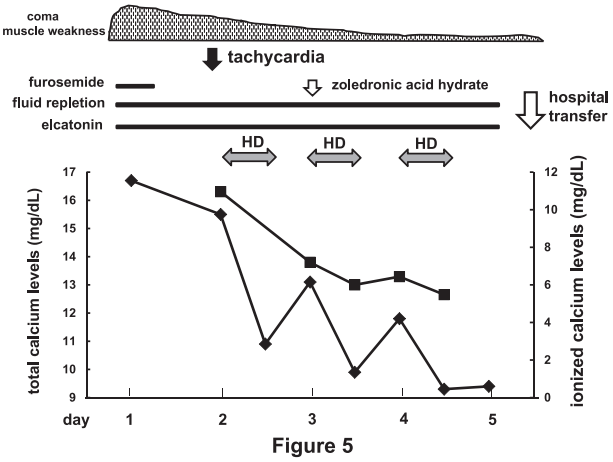

Fig. 5. Clinical course. Total calcium levels are indicated by diamond blocks and ionized calcium levels are indicated by square blocks. HD, hemodialysis.

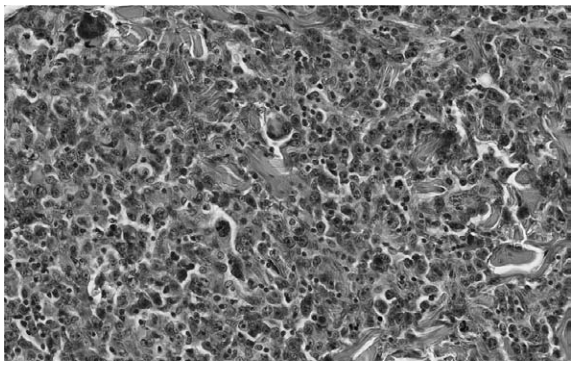

Fig. 6. Hematoxylin and eosin stain of the dermis reveals a dense infiltrate of atypical lymphocytes.

A biopsy of the right lower quadrant tumor was obtained, and treatment was initiated while awaiting the biopsy results. Fluids were replaced with 3 l of isotonic saline solution per day, and intravenous furosemide of 40 mg with 80 units / day of a calcitonin derivative, elcatonin, were administered intramuscularly to treat the hypercalcemia. Hemodialysis was initiated on the second hospital day, after no rapid effect of these treatments was observed and the patient had developed tachycardia of 150 beats / min. The dialysis time was 4 h, with a blood flow of 150 ml / min and a dialysate flow rate of 500 ml / min. The membrane area was 1.5 m^2 and the calcium concentration of the dialysate was 5 mg / dl. On the following day, 4 mg of the bisphosphonate, zoledronic acid hydrate, was administrated by intravenous injection. The patient's serum calcium concentration levels decreased after hemodialysis. His total calcium level decreased from 16.7 mg / dl to 9.3 mg / dl, and ionized calcium level decreased from 11.0 mg / dl to 5.5 mg / dl. On the fifth day in hospital, his consciousness had improved and his medical condition was stable. On the eighth day in hospital, he was transferred to another hospital to begin chemotherapy (Fig. 5).

A review of the biopsy results revealed a dense dermal infiltrate of atypical lymphocytes in the hematoxylin and eosin-stained specimens. The subcutaneous adipose tissue was infiltrated by diffuse atypical lymphocytes. These cells had abundant cytoplasm and horseshoe-shaped nuclei, with prominent multiple or single nucleoli (Fig. 6). Immunostained specimens showed numerous neoplastic cells that stained positive for CD30 (Fig. 7A), and were negative for the ALK protein (Fig. 7B). This staining pattern is indicative of ALCL. The neoplastic cells stained positive for CD2, CD5, CD56 and epithelial membrane antigen (EMA), and were negative for CD3, CD4 and CD8. The final diagnosis for the patient was ALK-negative ALCL with hypercalcemia.

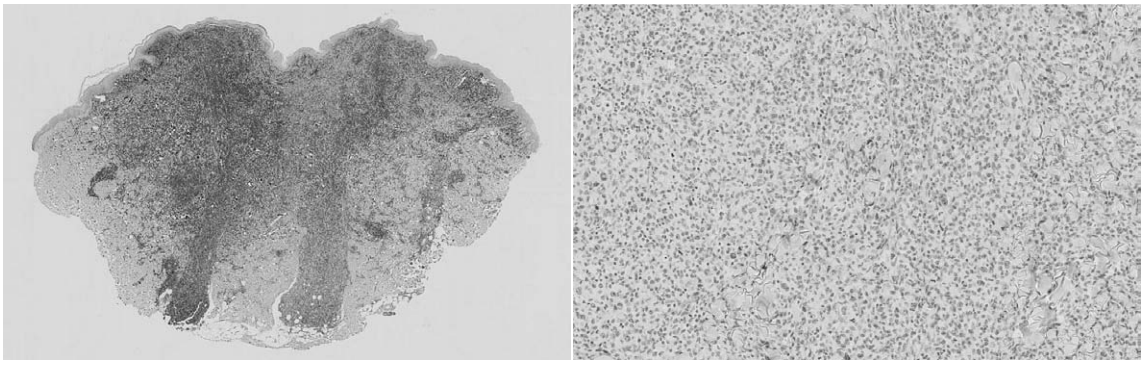

Fig. 7. Immunostaining of the dermis
A : Numerous neoplastic cells stained positive for CD30.
B : Numerous neoplastic cells stained negative for anaplastic lymphoma kinase protein.

Discussion

ALCL is a type of non-Hodgkin lymphoma (NHL) that represents approximately 2% of NHL cases in adults[3]. At present, malignant lymphomas are classified according to the fourth edition of the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues[4]. The type of disease is determined by cell morphology, origin of tumor cells, genetic abnormalities, chromosomal aberrations, and clinical characteristics.

ALCL is a T-cell lymphoma that consists of large lymphoid cells with abundant cytoplasm, horseshoe-shaped nuclei, and strong CD30 expression. The tumor is classified as primary cutaneous ALCL if it is confined to the skin in patients with no pre-existing lymphoproliferative disorder. ALCL can also be classified as primary systemic ALCL, which occurs in patients with systemic disease, and is further classified into ALK-positive ALCL and ALK-negative ALCL. Several retrospective studies have found that patients with ALK-negative ALCL have worse overall survival than those with ALK-positive tumors[5–7]. We diagnosed our patient with ALK-negative ALCL based on the presence of axillary lymphadenopathy, splenomegaly, skin tumor, bone infiltration, and ALK-negative status.

Laboratory investigations have found that 40% of patients with primary systemic ALCL have an elevated lactate dehydrogenase level, 30% have anemia, and 10% exhibit thrombocytopenia. The skin is the most common site of extranodal disease (25%), whereas other sites include the gastrointestinal tract, breast, spleen, liver, and bone[6, 8]. Our patient had thrombocytopenia and presented with extranodal disease of the skin, spleen, and bone.

Primary hyperparathyroidism and malignancy are the most common causes of hypercalcemia, and account for more than 90% of cases[9, 10]. Moreover, hematologic malignancies account for 15% of malignancy-associated hypercalcemia cases[11]. Several types of NHL are prone to hypercalcemia, including adult T-cell leukemia / lymphoma and diffuse large B-cell lymphoma with hypercalcemia, but we could not find any reports of this complication in ALCL.

Hypercalcemia in patients with cancer primarily results from increased bone resorption and

the subsequent release of calcium into the circulation. There are three major mechanisms for tumor-derived hypercalcemia : osteolytic metastases causing local release of cytokines, otherwise known as local osteolytic hypercalcemia (LOH); tumor secretion of PTHrP, also termed humoral hypercalcemia of malignancy (HHM); and tumor production of 1,25-dihydroxyvitamin D_3 (active vitamin D)[2, 12-14]. Hypercalcemia of malignancy by LOH is less common with NHL[2, 13], whereas HHM and tumor production of active vitamin D are more commonly noted[9, 13, 15]. Initially, we hypothesized that the hypercalcemia in this patient resulted from HHM, given his elevated levels of PTHrP and low levels of active vitamin D. The tumor infiltration of bone suggests that LOH coexisted with HHM, which may have caused the notable hypercalcemia.

Typically, the first intervention in a patient with hypercalcemia is fluid replacement with isotonic saline solution. This treatment needs to be supplemented in most cases with medications, including calcitonin and bisphosphonates, because its effect is transient. Calcitonin is a calcium regulatory hormone that strongly inhibits the bone-resorbing activity of osteoclasts[16]. Bisphosphonates bind to exposed hydroxyapatite on bone surfaces, particularly those undergoing active resorption. When osteoclasts begin to resorb bone impregnated with bisphosphonates, they become impaired because of the resulting release of the bisphosphonate[17-20]. Glucocorticoids inhibit the production by the tumor of locally active cytokines that have direct osteolytic effects[1, 2, 11, 12]. If the coexistence of LOH were definitely established then the curative effect would be higher by the use of combination steroid therapy.

Hemodialysis with low-calcium or calcium-free dialysate is recommended in cases where fluid replacement with isotonic saline and medical therapy does not affect the hypercalcemia[1]. It should also be used if the patient has renal failure or is in a coma[1]. As neither the hypercalcemia nor the coma in this patient improved with the initial treatment, hemodialysis with a low-calcium dialysate was initiated. Prompt control of serum calcium levels and treatment of the underlying disease are important for the patient's prognosis in the treatment of hypercalcemia of malignancy[21]. We suggest that the control of this patient's calcium levels with hemodialysis contributed to the positive outcome. Both low-calcium and calcium-free dialysate solutions are used in hemodialysis for hypercalcemia[22-26]. It should be noted that calcium-free hemodialysis solutions are responsible for the major adverse event of hypotension in 35% of sessions[23]. This complication is probably due to a rapid decline in calcium level that results in the elimination of the vasoconstrictor effect of the mineral. In Japan, most commercially available dialysates contain calcium levels of 5.0 to 7.0 mg / dl. We selected the lower dialysate concentration, and the patient's blood pressure after hemodialysis decreased from 155 mm Hg to 120 mm Hg, which was mild. The most effective concentration for hemodialysis treatment for hypercalcemia has not yet been established and further studies of dialysate calcium concentrations are needed.

In summary, we report the rare complication of hypercalcemia in a patient with ALK-negative ALCL. The patient recovered well from the coma of hypercalcemia with malignancy, after combined hemodialysis and medical therapy.

Conflict of interest

The authors have declared no conflict of interest.

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