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Non-Hodgkin's Lymphoma Complicated with Marked Hypercalcemia Caused by Parathyroid Hormone Related Protein, Presenting with Adams-Stokes Attack

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Abstract A rare case of non-Hodgkin's lymphoma (NHL) complicated with marked hypercalcemia caused by parathyroid hormone related protein (PTHrP) and presenting with Adams-Stokes attack is reported. A 72-year-old woman was involved in a traffic accident, and was transferred to our hospital. Blood examination revealed marked hypercalcemia (5.3 mmol/l (21.3 mg/dl)). A diagnosis of NHL (B-cell lymphoma, clinical stage IVA) was made by the results of the bone marrow biopsy, CT features showing multiple masses, and the gallium scintigraphy showing strong accumulation. Because of high blood level of PTHrP, hypercalcemia was considered to be due to PTHrP as a mediator acting on calcium metabolism. Hypercalcemia complicated with malignancy has a risk resulting in a fatal outcome. In the cases of malignant lymphoma complicated with hypercalcemia, we should pay attention to PTHrP as a mediator.

Keywords: *lymphoma, hypercalcemia, parathyroid hormone related protein*

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1. Introduction

Hypercalcemia is one of the complications of malignant tumor. Malignant lymphoma complicated with hypercalcemia caused by parathyroid hormone related protein (PTHrP) as a mediator acting on calcium metabolism is rare. We report a patient with non-Hodgkin's lymphoma (NHL) accompanied by marked hypercalcemia caused by PTHrP, and presented with Adams-Stokes attack.

2. Case Presentation

A 72-year-old woman was involved in a traffic accident during driving a car. Her car collided with a building, and the air bag of her car swelled out. After the accident, she was found to be in coma when an ambulance arrived. No witness was noted at the scene. She could not remember the accident. The details of the accident were unknown. She was transferred to the emergency room of our hospital, and was admitted for a close inspection. She had a history of sciatic neuralgia (43-year-old) and myringoplasty (59-year-old). She took no medicine. Her clinical course is shown in Figure 1. On the admission, her consciousness was Glasgow Coma Scale E4V5M6, body temperature was 38.2°C, blood pressure was 123/67 mmHg, pulse rate was 89 beats/minute, oxygen saturation was 90% in the room air, superficial lymph nodes and hepatosplenomegaly were not palpable. External signs of trauma were absent. During the medical examination, she developed sudden onset of a convulsive seizure with a conjugate deviation to the upper-right side, and tremors of her arms was observed for ten seconds. On the electrocardiogram monitoring at this time, sinus arrest was found, making a diagnosis of Adams-Stokes attack. A temporary external pacemaker was introduced to treat the sinus arrest. An examination of 12-lead electrocardiogram at this time failed to reveal shorting ST interval and ischemic change. Cardiac echo did not show a motion disorder of cardiac wall, a pericardial fluid effusion, and a neoplastic mass. Laboratory data on admissionis shown in Table 1. Results of blood examination were as follows: white blood cell count 6300 /μl, atypical lymphocytes accounted for 2.5%, anemia (Hemoglobin 10.5 g/dl), thrombocytopenia (Platelet count 103000 /μl), hyperfibrinolysis (D-dimer 23.9 μg/ml), serum potassium (2.8 mEq/l), marked hypercalcemia (5.3 mmol/l (21.3 mg/dl)), and negative HTLV-1 antibody. Serum calcium level was corrected as following formula: corrected serum calcium level (mg/dl) = serum calcium

level (mg/dl) - serum albumin level (g/dl)+4.). As shown in Figure 2 (a), her head Computed Tomography (CT) revealed a mass lesion located from the left maxillary sinus to the pharyngeal cavity, and no traumatic change was noted. On the second day of admission chest and abdominal CT showed multiple masses located on the left submaxillary region, left adrenal gland, leftrenal hilus, right renal pelvis, and right pelvis (Figure 2 (b-d)). Because of these CT findings, strongly suggesting malignancy, the hypercalcemia was considered to be caused by malignant tumors. We started to treat the hypercalcemia with fluid replacement, and administration of bisphosphonate and calcitonin. As the cause of her sinus arrest, existence of myocardial ischemia was suspected. Myocardial fatty acid metabolism scintigraphy failed to reveal decreased uptake of fatty acid as a sign of myocardial ischemia. On the sixth day of admission, an implantable pacemaker was introduced. The laboratory data revealed that the blood level of PTHrP was high (2.9 pmol/l) and that of parathyroid hormone was low (7 pg/ml). On the seventh day of admission, fine needle aspiration biopsy of the left mandibular lymph node was carried out, and the result of biopsy was classIII, making the pathological diagnosisof the lymph node incomplete. On the eighth day of admission, serum calcium was normalized to the level of 2.7 mmol/l (9.1 mg/dl) by treatment. On the ninth day bone marrow biopsy revealed invasion of the atypical cells. The atypical cells had the immunophenotype of mature B cell and were positive for such as CD20, CD79α, BCL6, MUM1 (Figure 3). The chromosomal anomaly was complex karyotypes. On the 16th day gallium scintigraphy showed strong accumulation in both sides of the orbit, left submaxillary region, both sides of the breast, mediastina, para-aortic region, and right pelvis. Because of strong accumulationin the breast on the gallium scintigraphy, an existence of malignant tumor was suspected in her breast, but medical examination and breast echo failed to revealed findings of malignancy. A diagnosis of NHL (B-cell lymphoma, clinical stage IVA) was made by the results of the bone marrow biopsy, CT features showing multiple masses, and the gallium scintigraphy showing strong accumulation. On the 40th day CHOP therapy (cyclophosphamide 750/m^2 day1+doxorubicin 50/m^2 day1+vincristine 1.4/m^2 day1+prednisolone 50/m^2 day1-5) was started. The dosage of CHOP therapy was reduced to 33% for severe myelosuppression predictably due to her age and bone marrow invasion of the tumor cells. As the second course of chemotherapy, R-CHOP therapy (Rituximab 375mg/m^2+CHOP therapy) with the reduced dosage of 50% was introduced. After the chemotherapy, CT showed partial remission of NHL, and 4 courses of R-CHOP therapy were subsequently followed. The high serum level of calcium and PTHrP were noted only at the time of the admission without recurrence.

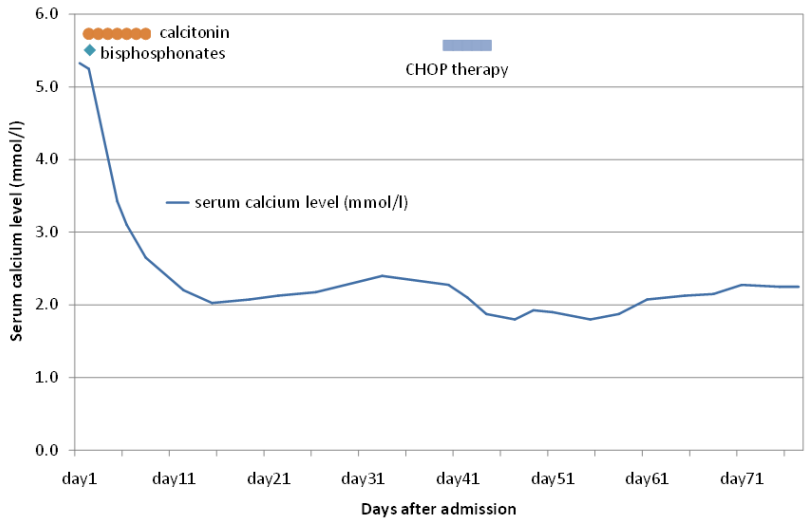

Figure 1. Clinical course after admission

Table 1. Laboratory data on admission

WBC	6300	/μl	TP	6.3	g/dl	soluble iL-2	4340	U/ml
Neu	71.5	%	Alb	3.6	g/dl	PTH intact	7	pg/ml
lym	18	%	Tbil	1.1	mg/dl	PTHrP	2.9	pmol/l
Mon	8	%	AST	59	IU/l	HTLV-1 Antibody	negative	
Atypical lym	2.5	%	ALT	28	IU/l			
RBC	3.27	×10^6/μl	LDH	486	IU/l			
Hb	10.5	g/dl	ALP	273	IU/l			
Ht	31.1	%	BUN	36.6	mg/dl			
MCV	95.1	fl	Cr	0.98	mg/dl			
MCH	32.1	pg	UA	12.7	mg/dl			
MCHC	33.8	g/dl	Amy	123	IU/l			
Plt	103000	/μl	CK	452	IU/l			
PTINR	1.12		Na	144	mEq/l			
aPTT	23.1	sec	Cl	104	mEq/l			
fibrinogen	241	mg/dl	K	2.8	mEq/l			
D-dimer	23.9	μg/ml	Ca	21.3	mg/dl			
			CRP	2.21	mg/dl			
			BS	122	mg/dl			

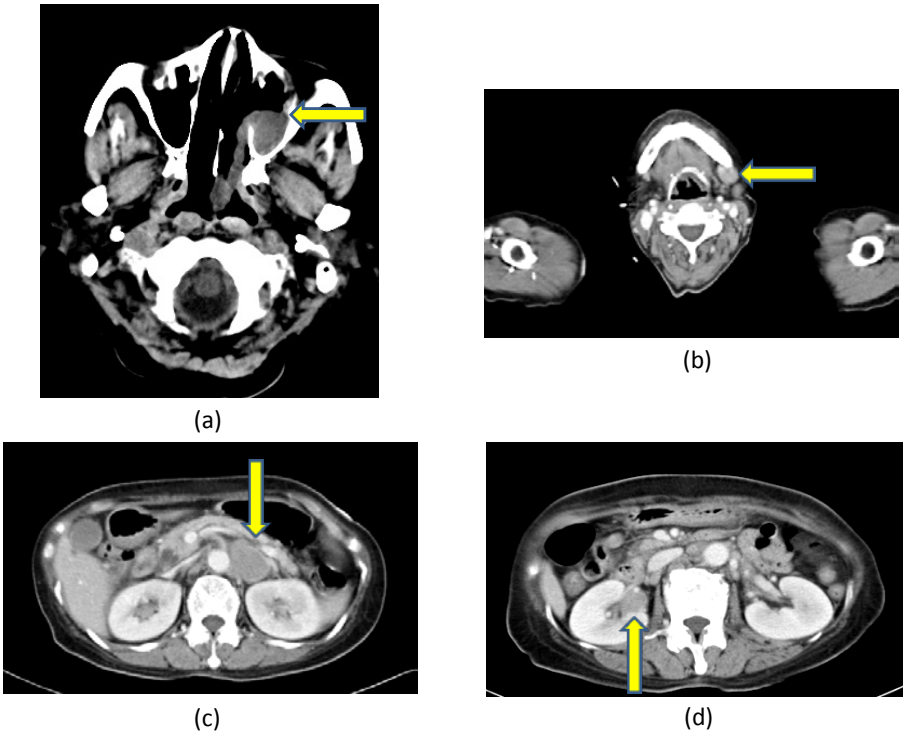

Figure 2. (a) Head CT showing the mass located from the left maxillary sinus to pharyngeal cavity, (b)(c)(d)Chest and Abdominal CT showing the multiple masses: (b)located on the left submaxillary region, (c)located onthe left•renal hilus region, (d) located onthe right renal pelvis region(arrow)

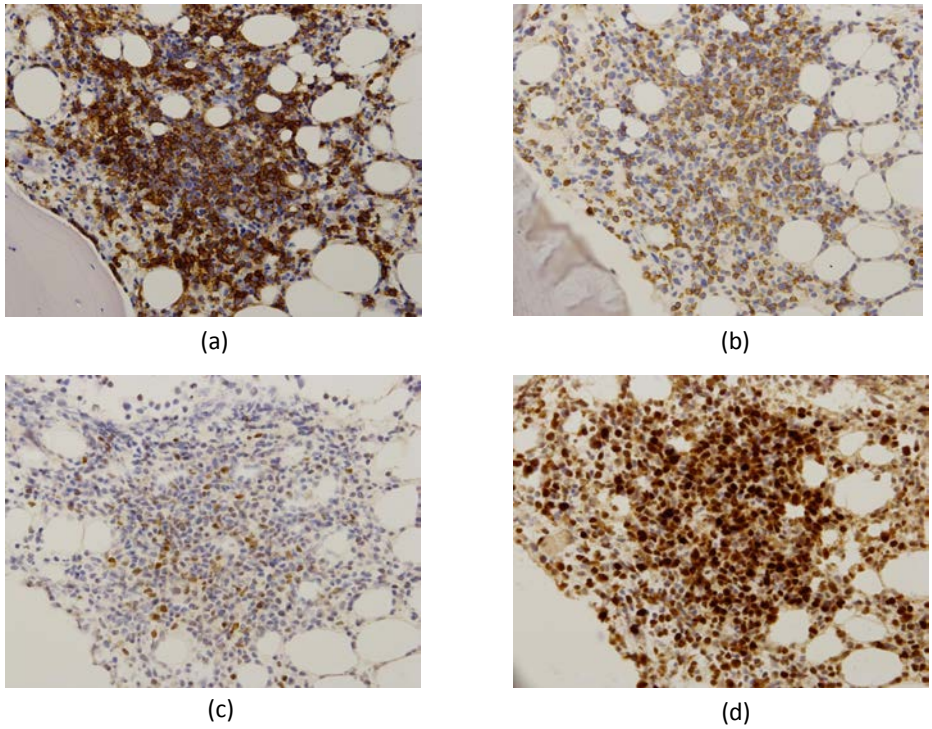

Figure 3. Bone marrow biopsy, immunostain of the atypical cells CD20 positive, (b) CD79a positive, (c)BCL6 positive, (d)MUM1 positive

3. Discussion

Hypercalcemia is one of the complications of a malignant tumor. When serum calcium level increases to 3.5 mmol/l (14.0 mg/dl) or more, in about 80% of causes various symptoms such as anorexia, nausea, vomiting, diuresis, polyposia, constipation, confusion, and coma were observed [1]. Kazama et al. reported a case of hypercalcemia complicated with renal failure, pancreatitis and hemorrhagic ulcer, resulting in fatal multiple organ failure [2]. Thus, hypercalcemia complicated with a malignant tumor may be resulted in fatal clinical course. In our case, because hypercalcemia was corrected immediately after presentation, preferable clinical outcome was obtained.

Hypercalcemia complicated with malignant tumor is roughly classified into two types. One type islocal osteolytic hypercalcemia (LOH) in which a malignant tumor invades a bone, and the local osteolysis by invasion causes hypercalcemia. Another is humoral hypercalcemia of malignancy (HHM) that is caused by a mediator such as PTHrP, PTH, calcitriol [1,25-$(OH)_2D_3$], acting on calcium

metabolism calcium metabolism. HHM is often observed in cases of solid tumors such as squamous cell carcinoma, renal carcinoma, ovarian cancer, and breast cancer. In these cases, PTHrP is often acting as a mediator. In most cases of HHM complicated with malignant lymphoma, calcitriol [1,25-$(OH)_2D_3$] is known to be acting as a mediator [3]. However, malignant lymphoma with hypercalcemia caused by PTHrP as a mediator is rarely reported. In our case, because of highblood level of PTHrP, a diagnosis of hypercalcemia due to PTHrP acting as a mediator was made.

There have been several reports of malignant lymphoma complicated with hypercalcemia caused by PTHrP as a mediator (Table 2). All of these cases are same as our case that is B-cell lymphoma, and that hypercalcemia is corrected by initial treatment. However, it is characteristic in our case that the patient presented with Adams-Stokes attack. The cases of malignant lymphoma presenting with sinus arrest are reported [8,9]. All of the cases are known to be secondary to cardiac invasion of malignant lymphoma. In our case, because cardiac invasion of malignant lymphoma was not detected, the association of malignant lymphoma and sinus arrest may require another explanation. Although myocardial ischemia and hyperkalemia are known as frequent causes of sinus arrest, both of them were excluded in our case. In general, as a cardiac complication of hypercalcemia, electrocardiographic shortening of ST interval is well known, but sinus bradycardia is not recognized [10]. However, there have been a report of a patient presenting with sinus bradycardia due to hypercalcemia [11]. As a possible cause of sinus arrest, hypercalcemia might be included. Although further elucidation is mandatory, there remains the possibility that hypercalcemia is associated with sinus arrest. Importance of this phenomenon deserves to be born in mind in clinical practice.

Table 2. Reports of malignant lymphoma with hypercalcemia caused by PTHrP as a mediator abbreviations: female: F; male: M; non-Hodgkin's lymphoma: NHL

Age	Sex	Disease (lineage)	On admission Ca (mmol/l)	On admission Ca (mg/dl)	PTHrP (pmol/l)	Treatment	Reference	Publish year
93	F	NHL (B cell)	4.2	16.6	5	calcitonin, bisphosphonates	4)	2003
85	F	NHL (B cell)	3.3	13.3	not available	calcitonin, bisphosphonates	5)	2010
71	M	NHL (B cell)	3.7	14.9	113	bisphosphonates	6)	2011
58	M	NHL (B cell)	3.6	14.4	5.7	not written	7)	2011

4. Conclusion

Hypercalcemia complicated with malignancy may be resulted in fatal clinical course. In the cases of malignant lymphoma complicated with hypercalcemia, we should pay attention to PTHrP as a mediator acting on calcium metabolism.

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Competing Interests

The author have no competing interests.

List of Abbreviations

parathyroid hormone related protein: PTHrP; non-Hodgkin's lymphoma: NHL; CHOP therapy: cyclophosphamide 750 /m^2 day1+doxorubicin 50 /m^2 day1+vincristine 1.4 /m^2 day1+prednisolone 50 /m^2 day1-5; R-CHOP therapy: Rituximab 375mg/m^2+CHOP therapy; local osteolytic hypercalcemia: LOH; humoral hypercalcemia of malignancy: HHM; female: F; male: M

References

[1] Sargent JT, Smith OP. Haematological emergencies managing hypercalcaemia in adults and children with haematological disorders. Br J Haematol. 2010; 149 (4): 465-77.

[2] Kazama JJ, Yamamoto T, Oya H, Yamamoto S, Sato Y, Sakurada J, Honda T, Endoh H, Narita I. A patient with severe hypercalcemia in multiple organ dysfunction syndrome: role of elevated circulating 1alpha, 25(OH)2 vitamin D levels. J Bone Miner Res. 2010 Jun; 25 (6): 1455-9.

[3] Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005 Jan; 352 (4): 373-9.

[4] Ota H, Azuma K, Horiuchi T, Kazama H, Araki A, Hosoi T, Sawabe M, Amizuka N, Orimo H. An elderly case of non-Hodgkin's lymphoma (NHL) with hypercalcemia [Article in Japanese]. Nihon Ronen IgakkaiZasshi. 2003 Mar; 40 (2): 167-71.

[5] Ghazi AA, Attarian H, Attarian S, Abasahl A, Daryani E, Farasat E, Pourafkari M, Tirgari F, Ghazi SM, Kovacs K. Hypercalcemia and huge splenomegaly presenting in an elderly patient with B-cell non-Hodgkin's lymphoma: a case report. J Med Case Rep. 2010 Oct; 19 (4): 330.

[6] Chinen Y, Nakao M, Sugitani-Yamamoto M, Kiyota M, Horiike S, Kuroda J, Taniwaki M. Intravascular B-cell lymphoma with hypercalcemia as the initial presentation. Int J Hematol 2011 Dec; 94 (6): 567-70.

[7] Nakayama-Ichiyama S, Yokote T, Iwaki K, Takubo T, Tsuji M, Hanafusa T. Hypercalcaemia in diffuse large B-cell lymphoma with expression of both parathyroid hormone-related protein and its receptor. Br J Haematol. 2011 Jul. 154 (1). 2.

[8] Motto A, Ballo P, Zito D, Cadenotti L, Moroni M, Dessanti P, Fedeli F. Primary cardiac lymphoma presenting as sick sinus syndrome. J ClinOncol. 2008 Dec; 26 (36): 6003-5.

[9] Kamimura M, Tanabe N, Hojo M, Horiuchi T, Kudo K, Saitoh K. Malignant lymphoma demonstrating sick sinus syndrome. Intern Med 1998 May; 37 (5): 463-6.

[10] El-Sherif N, Turitto G. Electrolyte disorders and arrhythmogenesis. Cardiol J. 2011; 18 (3): 233-45.

[11] Badertscher E, Warnica JW, Ernst DS. Acute hypercalcemia and severe bradycardia in a patient with breast cancer. CMAJ. 1993 May; 148 (9): 1506-8.