

Case Study

Bilateral Adrenal Lymphoma with Hypercalcemia : An Autopsy Case Report with a Review of the Literature

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We report here an unusual autopsy case of bilateral adrenal lymphoma showing symptoms associated with hypercalcemia and taking a fulminant clinical course. The serum of the patient had a titer of 40 pg/ml of intact parathyroid hormone (normal range: 10-65 pg/ml) and a titer of 1720 pmol/l of parathyroid hormone-related protein (PTHrP) (normal range: 13.8-55.3 pmol/l). Autopsy revealed bilateral huge adrenal tumors, with the left weighing 230 g, and measuring 12×9×3.5 cm, and the right weighing 140 g and measuring 11×8×3 cm. Histological examination revealed that the adrenal tumors were diffuse large cell lymphoma, and that the neoplastic cells were positive for CD20 (L26) and CD79a (mb-1). In addition, the neoplastic cells were positive for PTHrP mostly in the perinuclear space of the cells. In addition to the coma associated with hypercalcemia and acute renal failure, congestion and bronchopneumonia developed, leading to the death of the patient. There have been three case reports of bilateral adrenal lymphoma associated with hypercalcemia. Hypercalcemia should be checked carefully in the cases with adrenal lymphoma because it may result in fulminant clinical course.

Key Words bilateral adrenal lymphoma, hypercalcemia, parathyroid hormone-related protein (PTHrP)

INTRODUCTION

Autopsy series have indicated lymphomatous involvement in the adrenal glands in about 25% of the patients with lymphoma^{1,2}. In contrast, the incidence of primary adrenal lymphoma is quite rare³⁻⁵. Primary adrenal lymphoma tends to be predominant in males compared to females (2.5 to 7 times), occurs with an average age of 61 years (38-81)⁶, a morphology of large cell lymphoma and a B-cell phenotype with a small number of T cell phenotype³⁻⁶. Of the 70 cases with primary adrenal lymphoma reported so far³,

bilateral cases constitute 70% of the total adrenal lymphomas⁴. In the cases of adrenal lymphomas, symptoms may occur, due to the tumor itself or adrenal insufficiency. In the previous reports, there have been three cases of bilateral adrenal lymphoma showing hypercalcemia⁵. However, the cause of this symptom has not been discussed. We present here an unusual case with bilateral adrenal lymphoma showing hypercalcemia probably due to parathyroid hormone-related protein (PTHrP) produced by lymphoma cells.

CASE REPORT

Clinical findings

A 73-year-old female subject had a strange behavior in the last 6 months. The patient had been suffering from hypertension and slight degree of aortic valvular disease since 1987. She complained about memory disturbance and weakness for walking, gradually experienced incontinence and drowsiness, and was admitted

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to the emergency ward of the hospital. At the time of admission, computed tomography indicated that she had bilateral adrenal tumors, measuring 10 cm on the left and 8 cm on the right. Biochemical serum examination revealed 3386 IU/l of lactic dehydrogenase (LDH). She was admitted to the hospital for detailed examination.

Biochemical data at the time of admission were as follows; white blood cells, 7600/ μ l; red blood cells, 417x10⁴/ μ l; hemoglobin, 12.1 g/dl; hematocrit, 36.3 %; platelets, 7x10⁴/ μ l; prothrombin time (PT), 13.6 sec; PT %, 84 %; total protein, 6.0 g/dl; albumin, 4.1 g/dl; total bilirubin, 2.16 mg/dl; glutamic oxaloacetic transaminase, 77 IU/l; glutamic pyruvic transaminase, 41 IU/l; LDH, 3386 IU/l; LDH isozyme (LDH1 26%, LDH2 37%, LDH3 26%, LDH4 7%, LDH5 4%); alkaline phosphatase, 205 IU/l; creatine phosphokinase, 169 IU/l; Na, 141 mEq/l; K, 2.7 mEq/l; Cl, 96 mEq/l; Ca, 27.2 mg/dl; blood urea nitrogen (BUN), 32.0 mg/dl; creatinin (Cr), 1.3 mg/dl; amylase, 351 U/l; CEA, 2.1 ng/ml; CA19-9, 13.2 U/ml; ACTH, 63 pg/ml; antidiuretic hormone, 34.0 pg/ml; cortisol, 29.5 μ g/dl; serum aldosterone, 48 pg/ml; soluble interleukin-2 receptor, 4170 U/ml, urinary vanillyl mandelic acid, 5.0 mg/day, urinary homovanillic acid, 3.5 mg/day; 17-KS, 7.3 mg/day, 17-OHCS, 17 mg/day.

At the time of admission, she was in a drowsy state, unable to walk, and unable to speak clearly. Superficial lymph nodes were not palpable. In addition to the bilateral adrenal tumors, hypercalcemia, high serum titer of LDH, and metabolic alkalosis, were noticed. Hypercalcemia was considered to be the main cause of the drowsiness, inability to walk, and general weakness. Needle biopsy was not carried out because of the poor general condition. Administration of a large amount of physiological saline, elcatonin and pamidronate disodium was initiated to correct for hypercalcemia. Fever and oliguria declared. Japan coma scale value was II-200. Five days after the admission, the serum calcium level improved to 13.1 mg/dl; however, respiratory condition deteriorated, with PCO₂ 59, PO₂ 80, PH 7.19, revealing combined acidosis. Tracheal intubation was then performed. She finally developed anuria and acute renal insufficiency (BUN, 160.6 mg/dl; Cr, 5.2 mg/dl). In spite of respiratory control with a respirator and fluid infusion,

the high fever continued with gradually deteriorated consciousness, and she died 7 days after admission.

Autopsy findings

Autopsy was performed 12 h after the patient's death. Slight degree of general jaundice was observed, and marked edema was seen in both the upper and the lower extremities. Superficial lymph nodes were not palpable.

Bilateral adrenal glands were markedly enlarged; 230 g in weight, 12×9×3.5 cm in size at right and 140 g in weight, 11×8×3 cm in size at left (Fig. 1). Macroscopically, these tumors had capsules and were generally brown in color admixed with small and large yellow-white nodules. On the cut surface, the tumors were smooth and glistening and had several large and small white

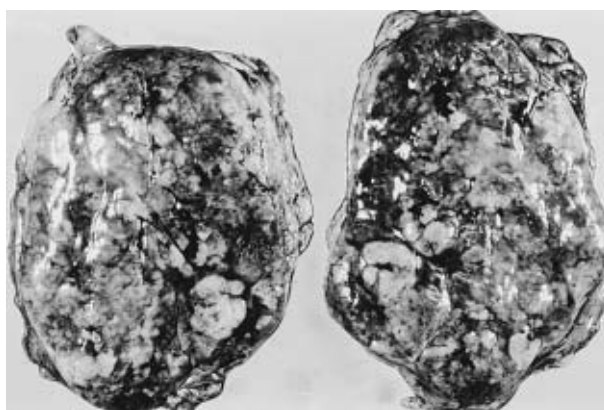


Fig. 1. Cut surface of bilateral adrenal lymphomas. Note the smooth and glistening surface with large and white nodules and dark red area accompanied by a severe congestion.

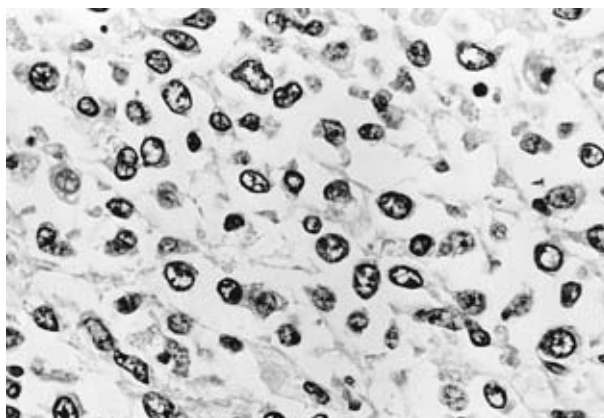


Fig. 2. H. E. staining. Large-sized lymphoma cells with round nucleus are observed. ×670

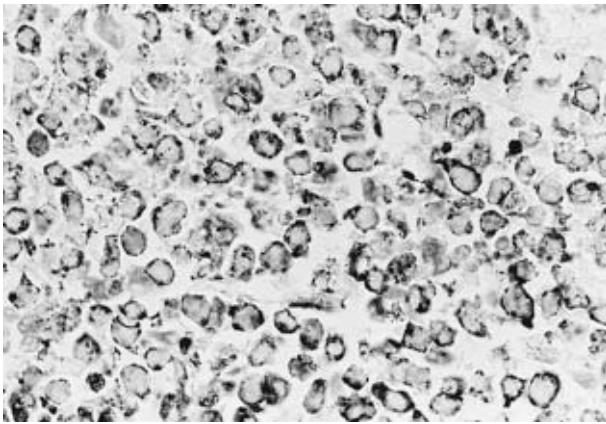


Fig. 3. Immunostaining for CD79a. Note the strong positive reactivity in the cytoplasm of the neoplastic cells. $\times 670$

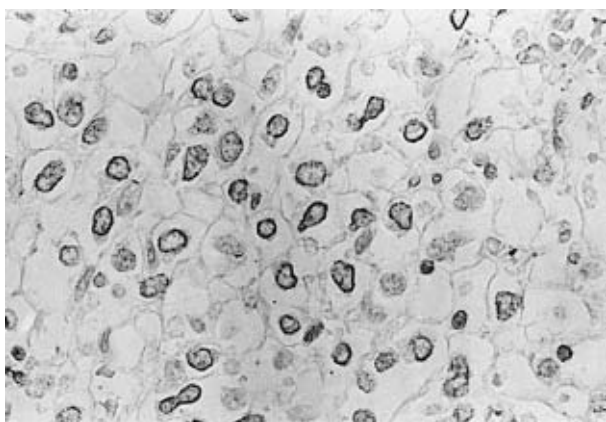


Fig. 4. Immunostaining for PTHrP. Positive reactivity is mainly observed in the perinuclear space of the neoplastic cells. $\times 670$

nodules. Histologically, the tumor showed monomorphous proliferation of large-sized lymphoid cells. The neoplastic cells were large in size with vesicular nucleus and coarse chromatin (Fig. 2). Several small nucleoli and ample cytoplasm were noticed.

Immunohistochemically, the neoplastic cells were positive for CD20 (L26) and CD79a (mb-1) (Dako, Copenhagen, Denmark), revealing a B-cell phenotype (Fig. 3). The neoplastic cells were positive for PTHrP (Calbiochem, Cambridge, USA) in their perinuclear spaces and occasionally on the cytoplasmic membranes (Fig. 4). Admixed with the neoplastic cells, remaining adrenal cortical cells were occasionally observed, and necrosis and calcification were also noticed.

Lymphomatous involvement was not obser-

ved anywhere outside the bilateral adrenal glands including lymph nodes. Calcification was observed in renal tubules, and mitral and aortic valves. While the former was considered to have been caused by hypercalcemia, the latter might have been accompanied by arteriosclerosis. The cause of the death of the patient was pulmonary edema concomitant with bronchopneumonia.

DISCUSSION

In the present case, severe hypercalcemia was observed at the biochemical examination, giving rise to various symptoms such as drowsiness, inability of walk, and general weakness. Blood examination performed at the time of autopsy revealed a normal level of intact parathyroid hormone (PTH) (40 pg/ml; normal value: 10–65 pg/ml), but the PTHrP level was extremely high (1720 pmol/l; normal value: 13.8–55.3 pmol/l). At the time of the autopsy, lymphomatous metastasis was not observed outside the adrenal glands, including the bones. Therefore, we consider that hypercalcemia was caused by the production of PTHrP by the neoplastic cells, based on the high serum levels of PTHrP and the positive reactivity of the neoplastic cells for the PTHrP immunostaining.

Hypercalcemia is often noticed in the patients having malignant neoplasia in the course of the disease. In hematological malignancies, hypercalcemia was observed in patients with adult T-cell leukemia/lymphoma (ATLL), multiple myeloma or malignant lymphoma in 23.5%, 26.7% and 5.6% of the cases respectively⁷. Hypercalcemia caused by malignant neoplasia is subclassified into local osteolytic hypercalcemia due to metastatic bone lesions and humoral hypercalcemia of malignancy (HHM) caused by the humoral agent produced by the neoplastic cells. Predominant cause of HHM is considered to be production of PTHrP. Of the malignant lymphomas, ATLL is well known as one of the PTHrP-producing tumors. Recent studies indicated that even in cases where the incidence of HHM is low in B-cell lymphomas, hypercalcemia is caused by PTHrP produced by the neoplastic cells^{8,9}. Al-Fiar et al⁵. reported that three out of 17 cases of adrenal lymphomas, including the cases they studied, were accompanied by hypercalcemia. However, the cause of this symptom has not been discussed so far. Although the

Table 1. Summary of a literature review of bilateral adrenal lymphoma.

Author	Age	Sex	Cell type	Treatment	Survival	Remarks
Salvatore et al(3)	27	M	Large non-cleaved B-cell	CHOP	CR	
Al-Fiar et al(5)	61	F	Diffuse large cell	CHOP	11 months	Hypercalcemia
Yamamoto et al(12)	63	M	Diffuse large B-cell	Surgery, Chemo	CR	ITP
Kuyama et al(13)	69	F	Diffuse mixed B-cell	CHOP	CR	Adrenal insufficiency
Wu et al(14)	64	F	Large immunoblastic B-cell	Surgery, Chemo	CR	
Ellis et al(15)	74	F	Diffuse B-cell	Chemo	3 weeks	Adrenal insufficiency
Frankel et al(16)	62	F	Anaplastic large cell	Surgery, Chemo	PR	EBER-ISH(+)
Hsu et al(17)	64	F	Diffuse large B-cell	Chemo	3 months	Adrenal insufficiency
Utsunomiya et al(18)	72	F	Diffuse large B-cell	Surgery, Chemo	12 months	Adrenal insufficiency
Hisano et al(19)	77	M	Angioendothelial lymphoma	Chemo, Rad	6 months	
Takahashi et al(20)	66	F	Diffuse large B-cell	Chemo	8 months	Adrenal insufficiency
Serrano et al(21)	71	M	Small cleaved cell	CHOP	CR	Addisonian crisis
Prayson et al(22)	69	F	Angiotrophic large cell	Steroid		Adrenal insufficiency
Pagliuca et al(23)	59	M	High grade B-cell	MACOP-B		Adrenal insufficiency
Abe et al(24)	68	M	Diffuse small and large cell			BM & PB involvement
Schnitzer et al(25)	74	M	T-cell immunoblastic	I.T.Methotrexate		
Shea et al(26)	81	M	Large cell	Steroid	2 months	Adrenal insufficiency
Osei et al(27)	55	M	Diffuse large cell			
Present case	73	F	Diffuse large B-cell		9 days	Hypercalcemia

F, female; M, male; Chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; Rad, radiation therapy; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; I. T. methotrexate, Intrathecal methotrexate; PR, partial remission; CR, complete remission; ITP, idiopathic thrombocytopenic purpura; ISH, in situ hybridization; BM & PB, bone marrow & peripheral blood

reason is still unknown, it is noteworthy that this lymphoma is frequently accompanied by hypercalcemia, including in this study.

PTHrP shares 8 out of the total 13 amino acid residues at the N-terminus (63%) in common with PTH. Also, PTHrP binds to the receptor (PTH/PTHrP receptor) with almost the same affinity as PTH, with a similar function. The PTH/PTHrP receptor is present in various organs of the body. In particular, it has an important role in the kidneys, where it enhances reabsorption of Ca, and has enhanced osteolytic function⁹⁻¹¹.

Symptoms accompanied by the production of PTHrP can be dependent on the degree of hypercalcemia or the speed of the onset of this symptom. In cases with hypercalcemia, regardless of the cause, weakness, depressive state, lack of attention, loss of appetite, nausea, vomiting, constipation, polyuria and polydypsia, reversible tubular dysfunction of the kidney, reduction of QT time, and arrhythmia may occur. The patient in the present case had a serum calcium titer of 27.2 mg/dl at presentation, and coma or acute renal insufficiency declared, accompanied with hypercalcemia. Furthermore, the patient had

congestion of lungs and bronchopneumonia, leading death.

Of the 70 cases with primary adrenal lymphoma reported so far³, bilateral cases constitute 70% of the total adrenal lymphomas⁴ (Table 1)^{3,5,12-27}. Correct diagnosis of primary bilateral lymphoma were made rarely before death, and most of the cases were not treated. Although intensive chemotherapy were given to the patients diagnosed with primary adrenal lymphoma, response to the therapy was not excellent. Although one of the reasons for the poor prognosis is the older age of the patients, other causes are yet to be identified⁵. Our patient died 9 days after the diagnosis of this lymphoma. However, in recent years, cases with long survival have been reported after performing chemotherapy or surgical extirpation¹²⁻¹⁴.

In conclusion, patients with primary adrenal lymphoma undergo a symptom free course and it takes a long time before correct diagnosis is made in most of the patients. Although quite rarely feasible as of today, correct diagnosis should be made early, and the patient should be treated as soon as possible to improve prognosis.

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