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Abstract

A patient with a diffuse, small cleaved cell, non-Hodgkin's lymphoma associated with marked hypecalcemia was described. Antibody to the adult T-cell leukemia-lymphoma virus was absent. Although bone marrow was infiltrated by lymphoma cells, destructive or lytic bone lesions could not be detected. The serum level of immunoreactive parathyroid hormone C-terminal (PTH-C) was normal. The serum level of 1, 25-dihydroxyvitamin D was lower than normal. This case suggests that other humoral substances produced by lymphoma cells may be responsible for hypercalcemia.

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— Brief Note —

A Case of Non-Hodgkin's Lymphoma Associated with Hypercalcemia

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A patient with a diffuse, small cleaved cell, non-Hodgkin's lymphoma associated with marked hypecalcemia was described. Antibody to the adult T-cell leukemia-lymphoma virus was absent. Although bone marrow was infiltrated by lymphoma cells, destructive or lytic bone lesions could not be detected. The serum level of immunoreactive parathyroid hormone C-terminal (PTH-C) was normal. The serum level of 1, 25-dihydroxyvitamin D was lower than normal. This case suggests that other humoral substances produced by lymphoma cells may be responsible for hypercalcemia.

Key words : **hypercalcemia, non-Hodgkin's lymphoma, bone resorption, parathyroid hormone (PTH), 1, 25-dihydroxyvitamin D**

Malignant lymphoma has not commonly been associated with hypercalcemia in spite of a high incidence of bone and marrow involvement. Canellos (1) reported that in 217 consecutive patients with malignant lymphoma, only 4 (1.8 %) had hypercalcemia, although 58 (26.7 %) had bone lesions and 63 (29.0 %) bone marrow infiltration. An incidence of hypercalcemia as high as 24-100 % was reported for patients with adult T-cell lymphoma (2, 3). Most patients with lymphoma-associated hypercalcemia have extensive bone involvement (1); however, only several well-documented cases without lytic bone lesions have been reported (4-8). The potential pathogenic mechanisms for hypercalcemia in malignant lymphoma have been debated. Some lymphomas may cause hypercalcemia by humoral factors including osteoclast-activating factor (OAF) (9-12), prostaglandins (13), parathyroid hormone (PTH)-like substance (14-18), 1, 25-dihydroxyvitamin D [1, 25-$(OH)_2$D] (4,19,20) and other undefined substances (14, 21).

In the present report, we describe a patient with non-Hodkin's lymphoma associated with marked hypercalcemia without destructive or lytic bone lesions, and discuss on the pathogenic mechanisms of lymphoma-associated hypercalcemia together with other reports.

Case Report

A 59-year-old man was admitted to Osaka Gyomeikan Hospital because of cervical and inguinal lymphadenopathy for the first time in July 1984. He had noticed cervical lymphadenopathy

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since June 1984. On admission, he did not have hepatosplenomegaly and cutaneous symptoms. The examination of a lymph-node biopsy specimen revealed a diffuse, small cleaved cell lymphoma (Fig. 1). Laboratory studies showed as follows: the red-cell count was 4,110,000; the hemoglobin was 14.2 g/dl; the hematocrit was 39.2 per cent; the white-cell count was 8,700 with 37 per cent lymphocytes without atypism, of which subpopulations were 84.5 per cent T-cells, 8.5 per cent B-cells, 6.5 per cent null-cells and 0.5 per cent double-marker cells; the platelet count was 261,000; the serum gamma-globulin level was 0.52 g/dl; the antibody to the adult T-cell leukemia-lymphoma virus (ATLA) was negative; and the serum calcium level was 4.9 mEq/l. X-ray films of the chest were normal. However, ^{67}Ga scintigram revealed involvement of bilateral hilar lymph-nodes. An electrocardiogram showed myocardial ischemia. As he had angina pectoris, it was difficult to use doxorubicin for the treatment. VEMP treatment (vincristine, cyclophosphamide, 6-MP and prednisolone) was started, and induced diminution of lymphadenopathy. The patient was discharged 3 months later and received the maintenance chemotherapy.

In May 1985, he was readmitted because of high fever and bilateral inguinal lymphadenopathy, and treated with prednisolone, antibiotics and gamma-globulin. As marked swellings of the right submandibular and bilateral inguinal lymph-nodes developed again, in October 1985 he was admitted for the third time. He responded well to the combination of VP (vincristine and prednisolone) therapy with the steroid mini-pulse therapy, but the steroid diabetes developed. As another aggressive chemotherapy was needed, the combined chemotherapy of a low dose of cis-dichlorodiammine-platinum (II) (CDDP) (50 mg at one time) with VP-steroid pulse therapy along with intravenous infusion of sufficient volume of water for getting good diuresis was performed twice on November 18 and December 23 in 1985. After that, rapid and marked diminution of lymphadenopathy was obtained.

In January, 1986, he was readmitted for the forth time, complaining of general fatigue and drowsiness with considerably swollen lymph-nodes. This time, symptoms of hypercalcemia were found. His biochemical profiles were as follows: the serum level of calcium was 7.1 mEq/l; phosphorus, 4.0 mg/dl; uric acid, 13.5 mg/dl;

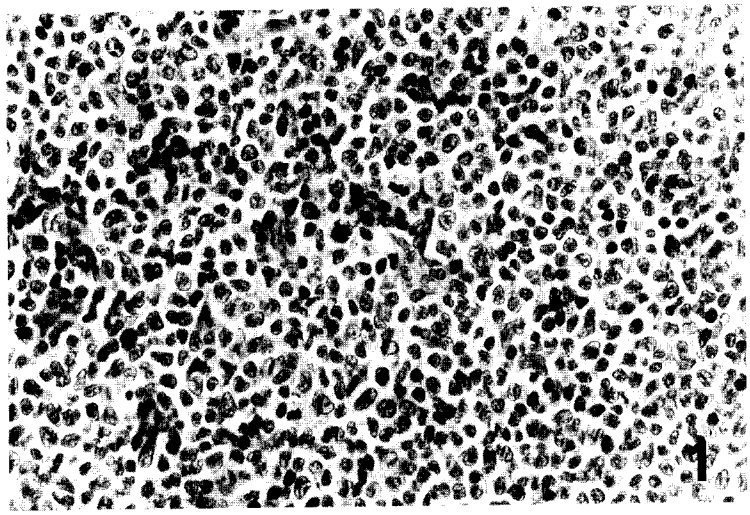

Fig. 1 Microscopic finding of the lymph-node specimen. Diffuse, small cleaved cells of non-Hodgkin's lymphoma were observed. Hematoxylin-Eosin stain, original magnification × 400.

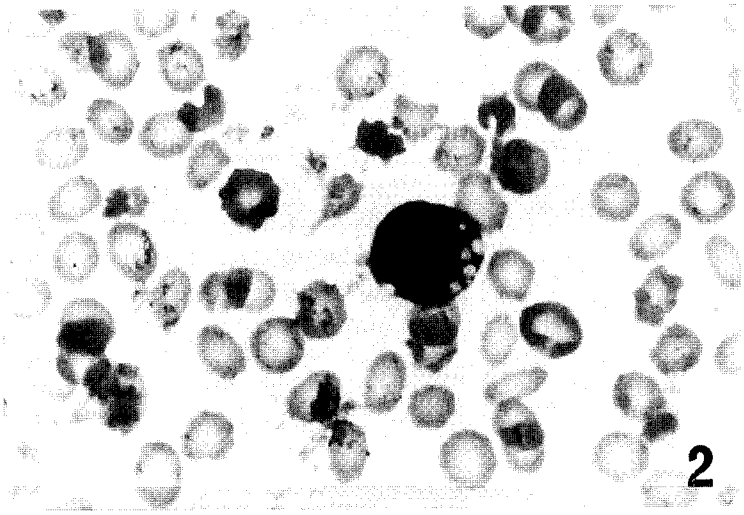

Fig. 2 A lymphoma cell with intracytoplasmic vacuoles in the bone marrow. Wright-Giemsa stain, original magnification × 1,000.

lactate dehydrogenase, 1,372 IU/l (with elevations of LDH 1, 2, 3 isozymes); urea nitrogen, 47.6 mg/dl; and creatinine, 1.8 mg/dl. The pancytopenia was found in the peripheral blood (red cells 2,660,000, platelets 50,000, white cells 2,700 with 76 per cent neutrophils, 4 per cent band forms, 1 per cent basophils, 1 per cent monocytes and 18 per cent lymphocytes without abnormal cells). In addition to hypercalcemia, renal failure progressed to serum levels of calcium and creatinine, 10.0 mEq/l and 4.7 mg/dl, respectively. Treatments with calcitonin, phosphate, steroid, diuretics and water infusion were ineffective for the hypercalcemia. The skeletal X-rays and bone scan did not show any destructive lesions or lytic bone lesions. A bone marrow examination from the iliac bone revealed massive infiltration (60.4 %) of lymphoma cells (Fig. 2), nevertheless leukemic lymphoma cells were scarcely observed in the peripheral blood. The serum level of immunoreactive parathyroid hormone determined by a carboxy-terminal radioimmunoassay (PTH-C) was 0.3 ng/ml (normal, 0.2–1.3 ng/ml). The serum level of 1, 25-$(OH)_2$D measured by a radioreceptor assay was 7 pg/ml (normal, 20–60 pg/ml). ATLA was reexamined and negative. Due to complication of disseminated intravascular coagulation, the patient died on Feburary 22, 1986.

Discussion

A patient with a diffuse, small cleaved cell, non-Hodgkin's lymphoma associated with hypercalcemia was reported. In the patient, ATLA was not detected. In all the cases with ATL-associated hypercalcemia so far reported, ATLA was found (3, 22, 23). A role of ATL virus in the pathogenesis of hypercalcemia was speculated (3, 22, 23). Very recently, Watanabe (24) has demonstrated that ATL cells express genes of parathyroid hormone-related protein (PTH-rP), which has been identified as a 141-aminoacid polypeptide (25–27). However, our case was indicated as having a B-cell lymphoma by histopathological findings. As an incidence of hypercalcemia in B-cell lymphoma is thought to be much lower than that in ATL (1–3), this case seems to be valuable to be reported. The striking clinical feature of this case was the presence of hypercalcemia associated with bone marrow infiltration, in spite of the absence of lytic bone lesions.

PTH and its C-terminal fragment (PTH-C) are partially metabolized by the kidney. Decreased glomerular filtration may raise the level of PTH-C, since its excretion route is only by filtration(18, 28). Despite the severe renal dysfunction, the serum level of PTH-C was not elevated in this case. This may suggest the presence of relative parathyroid suppression. However, a possibility could not be ruled out that lymphoma cells might produce a PTH-like substance, such as PTH-rP.

Recently, Breslau *et al.* (4) and Rosenthal *et al.* (19) have reported several lymphoma-associated hypercalcemia cases showing the elevation of circulating 1, 25-$(OH)_2$D. They have concluded that hypercalcelmia in some malignant lymphoma patients might be caused by the increased systhesis of 1, 25-$(OH)_2$D by lymphoma cells. In our case, the serum level of 1, 25-$(OH)_2$D was not elevated but markedly lowered, indicating that 1, 25-$(OH)_2$D was not responsible for this hypercalcemia and also that it could not be normally converted from 25-(OH)D in the kindney because of the severe renal dysfunction.

Cytokines, interleukins (IL-1α and IL-1β) and tumor necrosis factors (TNF-α and TNF-β), are known to have bone resorbing activity, and are also called osteoclast-activating factors (OAFs) (29–32). OAF may participate in the pathogenesis of hypercalcemia in this case.

CDDP has been widely used as an effective anti-tumor agent. CDDP is reported to have definite but moderate activity against advanced lymphoma (33), and to be useful as pare of a second line or salvage therapy for refractory non-Hodgkin's lymphoma (34, 35). In the present case, a combination chemotherapy of a low dose of CDDP with VP-steroid pulse therapy led to a quick tumor response. Hewever, the response was only transient, resulting in a fatal hypercalcemia. In addition to anti-tumor chemotherapy, development of a specific therapy on the basis of the pathogenesis of malignancy-associated hypercalcemia is required.

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