

## Pathogenesis of Metastatic Calcification due to Hypercalcemia in Adult T-cell Leukemia-Lymphoma

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**SUMMARY:** Two cases of metastatic calcification due to hypercalcemia in adult T-cell leukemia-lymphoma (ATLL) associated with osteolytic change for activation of osteoclasts are reported. These cases of serum calcium were at a high level, 16.2 and 19.4mg/dl (normal range 8.4-10.4mg/dl). In our cases, metastatic calcification was detected in the tubules of kidneys, in the pulmonary alveolar septa of lungs, in the myocardium, in the muscular layer of stomach, in the lower portion of media of aorta, in the mucosa of stomach, in the tubules of testis, and in the liver by von Kossa's silver nitrate method for calcium. Scattered osteoclasts were seen around the cortex of the bone. Roentgenograms showed osteolytic change in the skull, in the bilateral ulna, in the radius, in the humerus, in the tibia, and in the fibula. Therefore, hypercalcemia in ATLL may be caused by bone resorption-stimulating factors which promote the differentiation of osteoclast cells, resulting in calcium increases in the serum.

### INTRODUCTION

Adult T-cell leukemia (ATL) was first proposed as an entity by Takatsuki and his colleagues<sup>11, 12)</sup> in 1976, and it was recognized to be a malignant proliferation of peripheral T-lymphocytes. This disease is also called adult T-cell leukemia-lymphoma (ATLL), because of the leukemic lymphoma nature. ATLL is strongly associated with a type-C retrovirus infection, human T-cell lymphotropic virus type 1 (HTLV-1)<sup>3, 7, 10)</sup>. The clinical and hematological characteristics of this disease are following: (i) onset in adulthood; (ii) appearance of pleomorphic leukemic cells that have markedly

deformed nuclei and T-cell surface markers; (iii) acute and chronic leukemia with rapidly progressive terminal course; (iv) high incidence of skin involvement such as erythroderma and nodule formation due to the infiltration of neoplastic cells; (v) frequent accompaniment by lymphadenopathy, hepatosplenomegaly, hypercalcemia, and severe infections; (vi) absence of mediastinal tumor; (vii) some familial disposition; and (viii) exclusively limited location of patients' birth places, clustered in southwestern Japan, especially on Nagasaki, Kagoshima, Miyazaki and Okinawa districts which rate as endemic areas of ATLL than other districts in Japan<sup>1, 4, 6)</sup>

Patients with ATLL are known to be fre-

quently accompanied by hypercalcemia which is one of the most difficult problems to treat and often results in direct cause of early death<sup>3, 6)</sup>. The mechanisms of hypercalcemia in ATLL patients have not been clearly explained. We present here two autopsy cases of metastatic calcification due to hypercalcemia in ATLL associated with osteolytic change for activation of osteoclasts, and also discuss the mechanism of hypercalcemia due to ATLL. This investigation was undertaken as an extension of our previous works.<sup>8, 9)</sup>

## REPORT OF TWO CASES

*Case 1.* This case in part, was reported previously (10). A 66-year-old man, who was born at Nagasaki in Japan, was admitted to the Nagasaki Red Cross Hospital, complaining of sore throat and neck stiffness. A left cervical lymph node biopsy showed a diffuse infiltration of atypical lymphoid cells with irregular nuclei which was medium in size, and a diagnosis of malignant lymphoma, diffuse, medium-sized cell type was made. An anti-HTLV-1 titer in the serum was positive. Serum calcium was 19.4 mg/dl (normal range 8.4-10.4 mg/dl). At autopsy, infiltration of leukemic-lymphoma cells consisting of atypical lymphoid cells with irregular nuclei, were found in the bone marrow of lumber vertebra and sternum, in the rib, in both kidneys, in the esophagus, in the cerebrum of left basal ganglia, and in the liver. Severe metastatic calcification was seen in the pulmonary alveolar septa of both lungs in the tubules of both kidneys, in the myocardium, in the muscular layer of stomach, in the lower portion of media of aorta, in the tubules of testis, and in the liver. Bone resorption by scattered osteoclasts was observed around the cortex of the bone. There was no adenoma and no hyperplasia in the parathyroid gland. Ulcer with cytomegalic inclusion bodies were found in the esophagus and duodenum.

*Case 2.* A 52-year-old man, who was born at Nagasaki in Japan, was admitted to the Nagasaki University Hospital, complaining of headache and pain in both legs. The iliac bone marrow biopsy showed a diffuse infiltration of malignant lymphoma cells which were medium

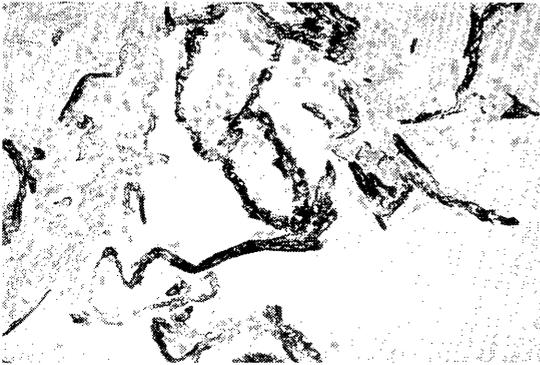
in size. An anti-HTLV-1 titer in the serum was positive. The serum was 16.2 mg/dl (normal range 8.4-10.4 mg/dl). At autopsy, infiltration of leukemic-lymphoma cells were found in the lymph nodes, in the bone marrow, and in the spleen. Severe metastatic calcification was seen in the pulmonary alveolar septa of both lungs, in the tubules of both kidneys, in the myocardium, in the muscular layer of stomach, in the mucosa of stomach, and in the lower portion of media of aorta. Scattered osteoclasts were seen around the cortex of the bone. The parathyroid gland was normal in histological section. Herpes infection was seen in the esophagus.

## MATERIALS AND METHODS

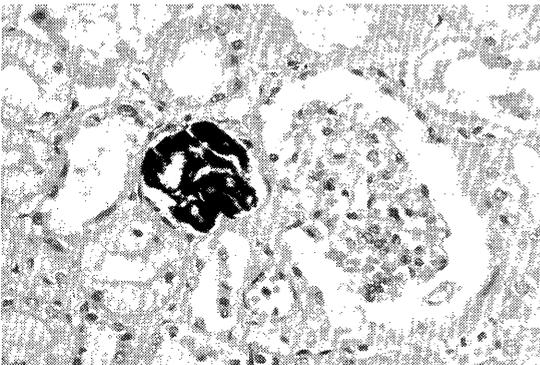
Two cases of metastatic calcification due to hypercalcemia in ATLL were studied by light microscope. The material in one case was derived from autopsy at the Nagasaki University Hospital and the other autopsy case was from the Nagasaki Red Cross Hospital in Nagasaki City. These autopsy cases were fixed in 10% formalin and were routinely embedded in paraffin. Paraffin-embedded 4 micron sections were stained with hematoxylin-eosin. Confirmation of calcium morphology was provided with von Kossa's silver nitrate method which widely used for demonstration of calcium.

## RESULTS

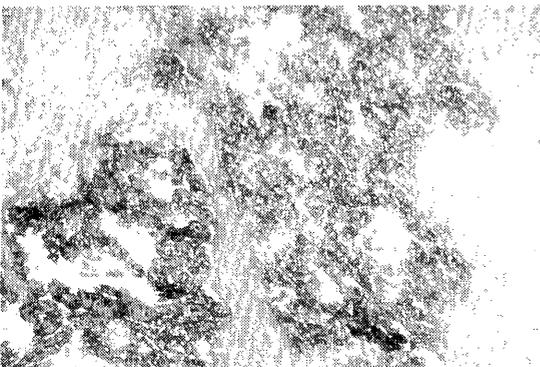
Metastatic calcification was observed in the pulmonary alveolar septa of lungs (**Fig. 1**), in the tubules of kidneys (**Fig. 2**), in the myocardium, muscular layer of stomach, and aorta. One out of 2 cases of metastatic calcification in the mucosa of stomach, in the tubules of testis, and in the liver. In the all cases, osteoclasts were observed around in the cortex of bone (**Fig. 4**). Osteolytic change was seen in the skull (**Fig. 5**), in the bilateral ulna, in the radius, in the humerus, in the femur, in the tibia, and in the fibula by X-ray photographs. These cases of serum calcium were at a high level, 16.2 and 19.4 mg/dl (normal range 8.4-10.4 mg/dl). All cases of parathyroid glands were normal in histological examination.



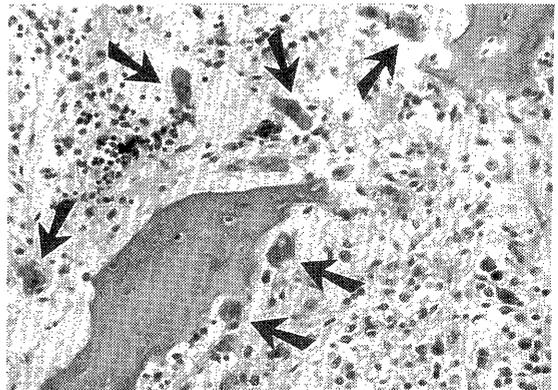
**Fig. 1.** Metastatic calcification are found in the tubules of kidneys. von Kossa's staining,  $\times 40$ .



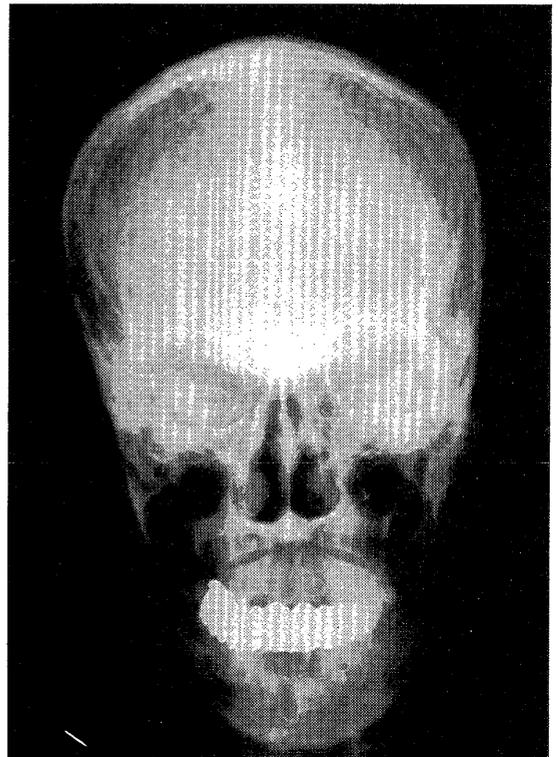
**Fig. 2.** Metastatic calcification are seen in the pulmonary alveolar septa of lungs. von Kossa's staining,  $\times 40$ .



**Fig. 3.** Metastatic calcification are observed in the myocardium. Hematoxylin and eosin staining,  $\times 40$ .



**Fig. 4.** Osteoclasts (arrows) found around the cortex of the bone, and infiltration of numerous leukemic-lymphoma cells are also observed in the bone marrow of vertebra. Hematoxylin and eosin staining,  $\times 400$



**Fig. 5.** Diffuse osteolytic changes are detected by skull roentgenogram.

## DISCUSSION

Hypercalcemia of neoplasm is caused by the action of tumor products on the bone to promote resorption and on the kidney to restrict calcium excretion. Two general mechanisms had been invoked to explain cancer associated hypercalcemia. Local osteolytic hypercalcemia is the result of bone resorption mediated by primary or metastatic tumor cells in direct contact with bone. Humoral hypercalcemia of cancer is the result of osteoclastic bone resorption mediated by circulating factors secreted by malignant cells which are remote from the bone. Humoral hypercalcemia of cancer could be distinguished clinically from primary hyperparathyroidism and local osteolytic hypercalcemia<sup>2)</sup>.

Hypercalcemia in patients with hematological cancers and other tumors without metastasis is probably due to the production of bone resorption-stimulating factors by the tumor cells. These bone resorption-stimulating factors include osteoclast-activating factor, 1,25-dihydroxyvitamin D, prostaglandins, parathyroid hormone-like substance, transforming growth factor, tumor necrosis factor, interleukin 1 alpha, colony-stimulating factor, and transforming growth factor-beta<sup>2, 3, 7, 10)</sup>.

Hypercalcemia has been reported to be a frequent complication of ATLL, which is one of the most difficult problems to treat and often results in the direct cause of early death<sup>3, 10)</sup>. Metastatic calcification due to hypercalcemia in ATLL was commonly seen in the alveolar septa of the lungs, and in the renal tubules<sup>4, 5)</sup>. In other diseases, metastatic calcification is often found in the lung and in the kidney.

The pathogenesis of hypercalcemia in ATLL patients are not clear. A possible explanation may be that the hypercalcemia in ATLL is caused by bone resorption-stimulating factors secreted by the malignant T-cells. They promote the differentiation of osteoclast precursor cells, thus, calcium increases in the serum. The present cases confirmed this theory, because bone marrow of our cases revealed marked activation of osteoclasts with infiltration of leukemic-lymphoma cells. Shirakawa

and co-workers<sup>10)</sup> stated that ATLL cells produced interleukin-1 which stimulated the activity of osteoclasts causing the release of calcium from bone and subsequently the high concentration of serum calcium works stimulatory on the growth of ATLL cells. On the other hand, a recent systematic study suggested that ATLL patients had humoral hypercalcemia of cancer with an increase of nephrogenous cyclin adenosine monophosphate (NcAMP) excretion and a suppression of 1,25-dehydroxyvitamin D. An increase of NcAMP excretion is regarded as a reflection of the interaction of the tumor-derived peptide with parathyroid hormone receptors in the proximal renal tubules<sup>3)</sup>. These results suggested that bone resorption-stimulating factors concurrently stimulate the activity of osteoclast.

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