

# Adult T-cell Leukemia-lymphoma associated with Metastatic Calcification and Acute Pancreatitis under Hypercalcemic Condition

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Metastatic calcification due to hypercalcemia in adult T-cell leukemia-lymphoma (ATL) associated with osteolytic change for activation of osteoclasts are reported. These cases of serum calcium were at a high level, 15.1 and 19.4 mg/dl (normal range 8.4-10.4 mg/dl). 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. ATL cells stained with parathyroid hormone-related protein (PTHrP) by immunohistochemical procedure. Thus, PTHrP is an important bone resorption-stimulating factor of hypercalcemia in ATL. We have investigated the incidence of acute pancreatitis in ATL, and in the other diseases. Of the 317,325 autopsy cases, 632 were ATL; the numbers of the acute pancreatitis cases of them were 1,833 (0.58%) and 25 (4.0%), respectively. The odds ratio from 2 x 2 table is 7.17 and Peason's Chi-square statistics with one degree of freedom is 126, which is highly significant. Therefore, it was suggested that there is a close correlation between acute pancreatitis and hypercalcemia in patients with ATL. We proposed a new theory for the correlation between acute pancreatitis and hypercalcemia in ATL that all the hypercalcemic patients exhibited high levels of nephrogenous cyclic adenosine monophosphate (NcAMP) stimulating pancreatic secretion in the extralobular ductal system of the pancreas and thus resulting in acute pancreatitis due to occlusion of the

pancreatic duct.

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**Key words:** adult T-cell leukemia-lymphoma, hypercalcemia, metastatic calcification, parathyroid hormone-related protein (PTHrP), acute pancreatitis

## Introduction

Adult T-cell leukemia-lymphoma was first proposed as an entity by Takatsuki and co-workers in 1977,<sup>1,2)</sup> and was then identified as a malignant proliferation of peripheral T-lymphocytes. This disease is also called adult T-cell leukemia-lymphoma (ATL) for its leukemic lymphoma nature. ATL is strongly associated with a type-C retrovirus infection, the human T-cell lymphotropic virus type-1 (HTLV-1).<sup>3,5)</sup> HTLV-1 infection causes ATL and a tropical spastic paraparesis/myelopathy.<sup>6,7)</sup> The clinical and hematological characteristics of this disease are as follows: onset in adulthood; appearance of pleomorphic leukemic cells that have markedly deformed nuclei and T-cell surface markers; acute and chronic leukemia with a rapidly progressive terminal course; high incidence of skin involvement, such as erythroderma and nodule formation, due to the infiltration of neoplastic cells; frequent concomitance with lymphadenopathy, hepatosplenomegaly, hypercalcemia and severe infections; absence of mediastinal tumor; some familial disposition; and exclusive geographic limitation to patients with birth place in the Caribbean and southwestern Japan, particularly Nagasaki, Kagoshima, Miyazaki and Okinawa districts, which are endemic area of ATL in Japan.<sup>8-10)</sup>

Patients with ATL are known to be at the same time frequently affected by hypercalcemia which is one of the most difficult problems to treat and often is a direct cause of early death<sup>3,8)</sup>. The authors present in this paper four autopsy cases of metastatic calcification in hypercalcemia due to ATL. We reported a case of ATL associated with acute pancreatitis due to hypercalcemia,

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we encountered three other cases of the same complication.<sup>15)</sup> The authors investigated the incidence of acute pancreatitis in ATL, and in the other diseases. The mechanism hypercalcemia in ATL patients have not been clearly explained. And also the mechanism of acute pancreatitis due to hypercalcemia in ATL patients have not been clearly explained. We discuss the mechanism of hypercalcemia in ATL and the mechanism of acute pancreatitis under hypercalcemic condition in ATL.

## Materials and Methods

### *Histochemical study*

Four cases of metastatic calcification due to hypercalcemia in ATL were studied by light microscopy. The material in 3 cases had been obtained from autopsies at Nagasaki University Hospital and in one case from 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 (HE). Confirmation of calcium morphology was provided by v. Kossa's silver nitrate method which is widely used for demonstration of calcium.

### *Immunohistochemical study*

Three cases of severe metastatic calcification due to hypercalcemia in ATL associated with osteolytic changes were studied by immunohistochemistry. The material was obtained at Nagasaki University Hospital from lymph nodes of autopsy cases. These specimens were fixed 10% formalin and were routinely embedded in paraffin. Paraffin embedded 4 micron sections were stained with parathyroid hormone-related protein (PTHrP) (Polyclonal antibody; Oncogene Science, Inc., New York; Lot. 93900202); this antiserum reacts with human PTHrP on immunoblots and formalin-fixed paraffin-embedded tissue sections, but shows no cross-reactivity with human parathyroid hormone. The antibody was diluted 1:10 with phosphate-buffered saline (PBS) pH 7.4. The indirect method was performed for the staining of PTHrP using Dako universal kit for polyclonal antibody (Dako PAP kit 548; Lot. 090-2).

### *Statistical analysis*

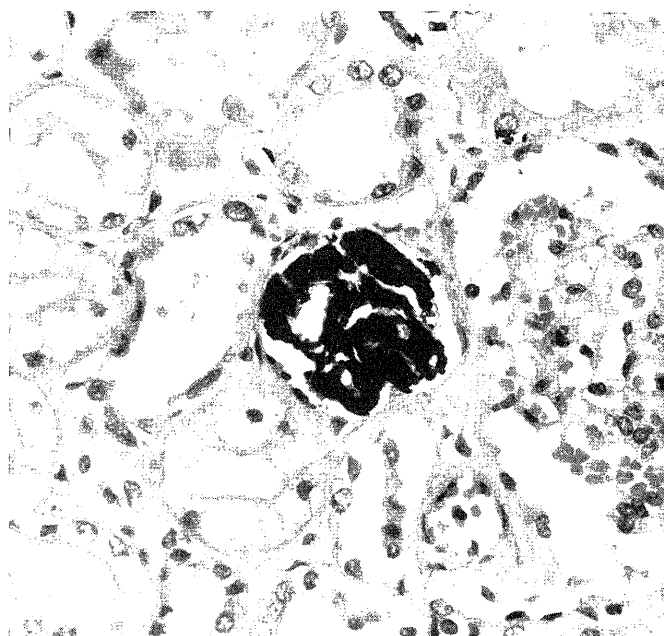
ATL, and acute pancreatitis cases were collected from the annual report of pathological autopsy cases in Japan in 1982-1989.<sup>11)</sup> Statistical calculation was performed. The statistical method for this study is the following: (1) Odds ratio to assess the degree of association between ATL and acute pancreatitis in a 2 x 2

contingency table. (2) Pearson chi-square test for the significance of the odds ratio in the contingency table.

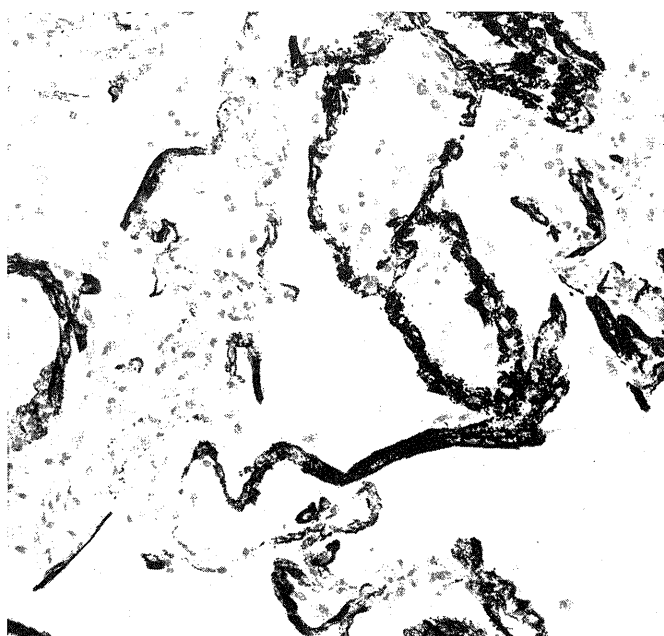
## Results

### *Histochemical study*

Metastatic calcification was observed both in tubules

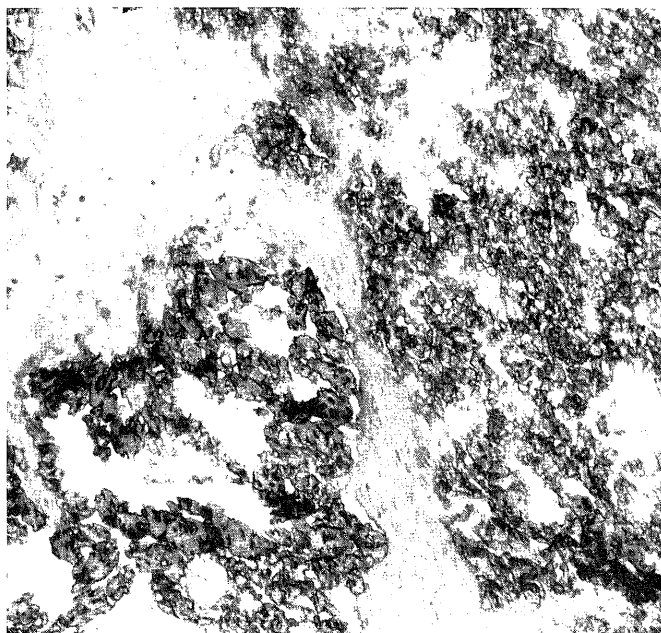


**Figure 1.** Metastatic calcification are found in the tubules of kidneys. von Kossa's staining, x200.

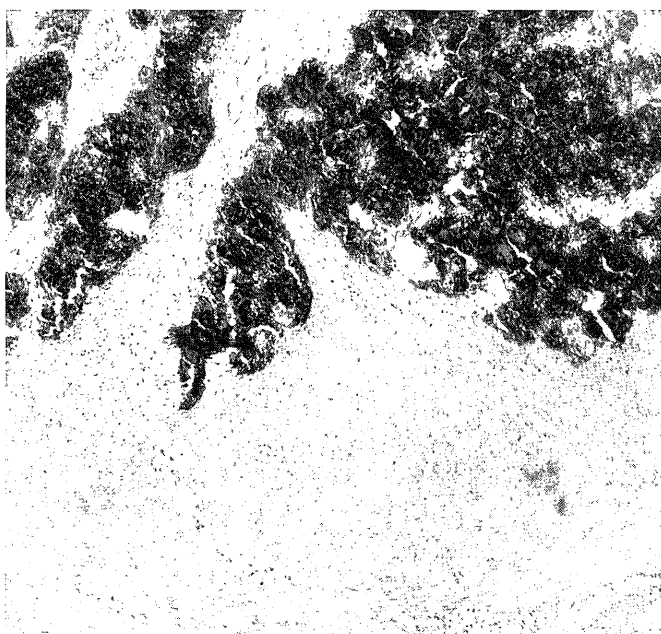


**Figure 2.** Metastatic calcification are seen in the pulmonary alveolar septa of the lungs. von Kossa's staining, x40.

of kidneys (Fig. 1) and in pulmonary alveolar septa of lungs (Fig. 2) in all cases described (100%). In 3 (75%) of the 4 cases metastatic calcification in the myocardium (Fig. 3) was detected. Furthermore it was detected in 2 (50%) of the 4 cases in the muscular layer of the stomach (Fig. 4) and in the media of the lower portion of the aorta (Fig. 5). In one case (25%) metastatic calcification was found in gastric mucosa



**Figure 3.** Metastatic calcification are observed in the myocardium. Hematoxylin and eosin staining, x40.



**Figure 4.** Metastatic calcification are detected in muscular layer of stomach. Hematoxylin and eosin, x40.

(Fig. 6), testicular tubules (Fig. 7), and liver (Fig. 8). These results suggested that renal tubule was the first organ to accumulate calcium, followed by pulmonary alveolar septa of lungs, myocardium, and muscular layer of the stomach (Table 1). Osteoclasts were observed around the cortex of bone in all cases (Fig. 9). Osteolytic change was seen in the skull (Fig. 10), in the bilateral ulna, in the radius, in the humerus, in

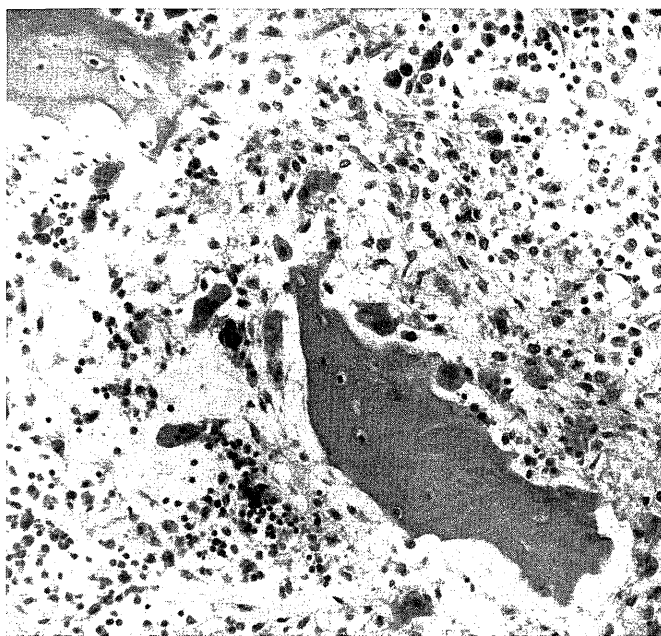


**Figure 5.** Metastatic calcification are seen in mucosa of stomach. Hematoxylin and eosin, x40.

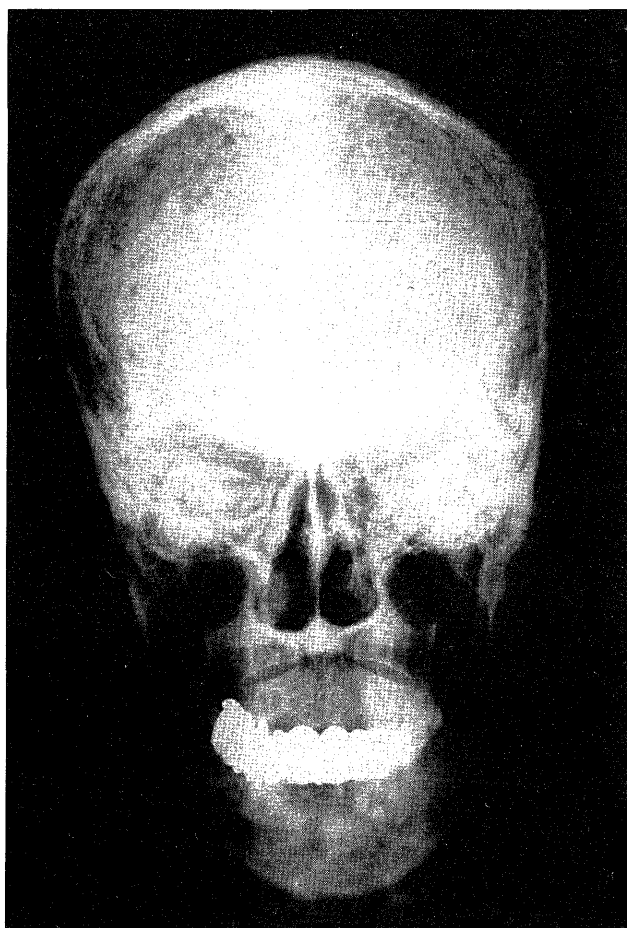


**Figure 6.** Metastatic calcification are found in aortic media. Hematoxylin and eosin staining, x40.





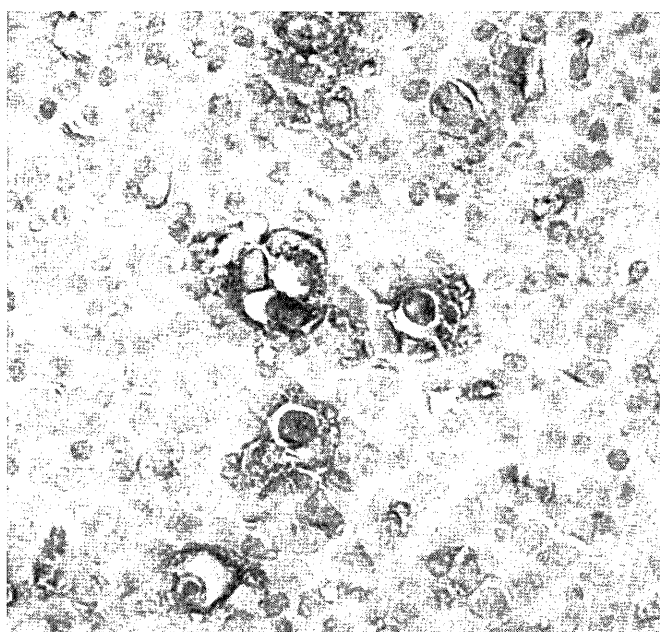
**Figure 9.** Osteoclasts found around of bone, infiltration of numerous leukemic lymphoma cells in bone marrow of vertebra. Hematoxylin and eosin, x200.



**Figure 10.** Diffuse osteolytic changes are detected by skull roentgenogram.

#### *Immunohistochemical study*

In all 3 cases, PTHrP was detected in ATL cells (Fig. 11). The pathogenesis of hypercalcemia in ATL patients is not clear. It may be caused by bone resorption-stimulating factors secreted by the malignant T cells, which promote the differentiation of osteoclast precursor cells. Our results support this theory. In addition, bone marrow of the patients showed marked activation of osteoclasts which may be due to production of PTHrP by ATL cells. Therefore, it is suggested that PTHrP is a humoral mediator of ATL associated hypercalcemia.



**Figure 11.** Immunoreaction for parathyroid hormone-related protein in leukemic-lymphoma cells in ATL. PAP method, x400.

#### *Statistical analysis*

Of the 317,325 autopsy cases in these years, 632 were ATL; the numbers of the acute pancreatitis cases of them 1,833 (0.58%) and 25 (4.0%), respectively. The odds ratio of the 2 x 2 table composed from these figures is 7.17 and Pearsons chi-square statistics with one degree of freedom is 126, which is highly significant. Figure 12 shows ATL associated with acute pancreatitis cases. The male to female ratio was 16:9 in ATL with acute pancreatitis cases. The highest incidence of ATL associated with acute pancreatitis cases was found in the 61-70 year-old age group (Fig. 12).

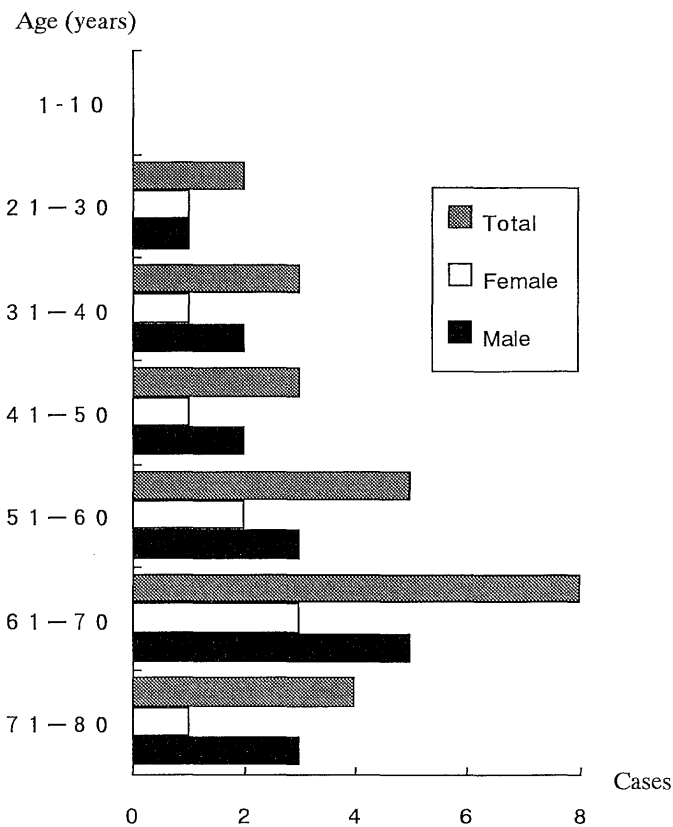


Figure 12. Age distribution of adult T-cell leukemia-lymphoma with acute pancreatitis

**Discussion**

Hypercalcemia of a neoplasm is caused by the action of tumor products on bone to stimulate resorption, and on 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 the 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 can be clinically distinguished from primary hyperparathyroidism and local osteolytic hypercalcemia.<sup>12)</sup>

The major organs involved in disruptions of calcium homeostasis in hypercalcemia of cancer are bone and kidney. Most patients with hypercalcemia of cancer have increased osteoclastic bone resorption and renal tubular reabsorption of calcium, similar to those with primary hyperparathyroidism. A more likely possibility is that the effects of the PTHrP on target organs are modified by other factors, such as transforming growth factor alpha (TGF-alpha), interleukin-1, and tumor

necrosis factor (TNF). Normal immune cells that produce potent osteotropic cytokines such as TGF-beta, interleukin-1, and TNF may occupy a pivotal role in the regulation of normal bone remodeling. These factors are all more powerful bone-resorbing factors than parathyroid hormone (PTH) resulting in increases serum calcium. Since these factors are often produced by tumors, which also produce PTHrP, hypercalcemia in these circumstances is probably due to the combined effects of PTHrP and these factors on target organs. These factors act synergistically with PTH and probably also with PTHrP to stimulate bone resorption because their major effect is to stimulate proliferation of osteoclast progenitors.<sup>13)</sup>

Metastatic calcification, due to hypercalcemia, in ATL was commonly seen in alveolar septa of the lungs, in renal tubules and in myocardium. Available data suggest that renal tubules are the first organs to accumulate calcium, followed by the pulmonary alveolar septa of the lungs and the myocardium.<sup>14-16)</sup> Unusual sites of metastatic calcification have been reported in the muscular layer of the stomach, mucosa of the stomach, aorta, tubules of the testis, in the liver, in the tongue, in the spleen, in the pancreas and systemic arterial walls.<sup>14-18)</sup> These cases of serum calcium were at a high level. The pathogenesis of hypercalcemia in ATL patients is not clear. A possible explanation may be that hypercalcemia in ATL is caused by bone resorption stimulating factors secreted by malignant T-cells.<sup>3,5)</sup> These factors stimulate the differentiation of osteoclast precursor cells and, consequently, calcium levels increase in the serum. This theory has been confirmed by cases reported previously; the bone marrow of patients in our study revealed marked activation of osteoclasts with infiltration of leukemic lymphoma cells.<sup>16)</sup>

PTHrP are a novel class of peptide hormone, isolated and cloned in 1987.<sup>19-21)</sup> These protein share marked amino-terminal homology with PTH and bind to a common PTH-PTHrP receptor.<sup>22, 23)</sup> PTHrP were first isolated from tumors associated with the syndrome of humoral hypercalcemia of cancer.<sup>24)</sup> Specifically, PTHrP bind to PTH receptors and stimulate adenylate cyclase in these tissues and also stimulate osteoclastic bone resorption. The findings that PTHrP stimulate nephrogenous cyclin adenosine monophosphate (NcAMP) production and stimulate bone resorption provide evidence that PTHrP are capable of reproducing the two other hallmarks of the clinical humoral hypercalcemia of cancer, namely, increases in NcAMP excretion and in osteoclastic bone resorption.<sup>24)</sup>

In contrast, the bone marrow of these patients showed marked activation of osteoclasts, which may be due to

the production of PTHrP by ATL cells.<sup>25)</sup> PTHrP has been implicated as a humoral mediator of hypercalcemia in malignant diseases.<sup>26, 27)</sup> The mechanism of hypercalcemia in ATL patients have not been clearly explained. However, it has also been suggested that PTHrP is the most important humoral mediator of ATL associated hypercalcemia.<sup>28)</sup> The osteotropic cytokines, such as TGF- $\alpha$ , interleukin-1 and TNF, are all powerful bone-resorbing factors and each increases serum calcium.<sup>4, 5)</sup> Increased osteoclastic bone resorption is obviously an important mechanism of hypercalcemia in ATL. Therefore, it is concluded that bone resorption stimulating factors concurrently stimulate the activity of osteoclasts. The kidney is also important in the development of hypercalcemia, which is almost always due to the impairment of renal function associated with a decrease in glomerular filtration and a decrease in the capacity of the kidney to clear the calcium load from the extracellular fluid.<sup>13)</sup>

ATL associated with acute pancreatitis due to hypercalcemia has been reported by Hosokawa and co-workers<sup>29)</sup> in 1984, Senba and co-workers in 1990,<sup>15)</sup> Dazai and co-workers<sup>30)</sup> in 1991 and Ono and co-workers<sup>31)</sup> in 1996. The authors are reported that there is a close correlation between acute pancreatitis and hypercalcemia in ATL.<sup>30)</sup> On the other hand, it may be that there is a close correlation between acute pancreatitis and hyperparathyroidism under hypercalcemic conditions. It has been estimated that 7-19% of patients in the USA who have parathyroid adenoma or parathyroid carcinoma are prone to developing acute pancreatitis.<sup>33,35)</sup> Moreover, a relationship between hypercalcemia and acute pancreatitis has been reported in different diseases that are associated with a high serum calcium level.<sup>36, 37)</sup>

The mechanism for the development of acute pancreatitis due to hypercalcemia in ATL is not clear. However, causes of acute pancreatitis due to hypercalcemia have been proposed based on the results of research into hyperparathyroidism. To date, the most plausible hypothesis, proposed by Kelly (1968)<sup>38)</sup> is that acute pancreatitis due to hypercalcemia is caused through the following sequence of events: increased serum calcium, rapid pancreatic juice calcium, accelerated calcium-dependent conversion of trypsinogen to trypsin and finally acute pancreatitis. Another possible explanation may be that all the hypercalcemic patients exhibited high levels of NcAMP<sup>3)</sup> stimulate pancreatic secretion in the extralobular ductal system of the pancreas<sup>39)</sup> and thus resulting in acute pancreatitis due to the occlusion of the pancreatic duct.<sup>32, 40, 41)</sup>

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