Adult T-cell Leukemia with Hypercalcemia-induced Metastatic Calcification in the Lungs Due to Production of Parathyroid Hormone-related Protein

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Abstract

A 60-year-old man was diagnosed as adult T-cell leukemia with severe hypercalcemia because of production of parathyroid hormone-related protein. After admission, the patient had respiratory insufficiency with an infiltrative shadow in his lungs suggestive of pneumonia. However, neither improvement in respiratory function nor disappearance of the abnormal chest shadow was observed with administration of various antibiotics. An autopsy demonstrated the chest shadow had been caused by metastatic calcification associated with hypercalcemia due to production of parathyroid hormone-related protein. The possibility of metastatic calcification should be considered in patients with adult T-cell leukemia and hypercalcemia who have an abnormal chest shadow.

Case Report

A 60-year-old man, born in Kagoshima prefecture located in southwestern Japan, was admitted to our hospital, complaining of general fatigue, anorexia, dysarthria and gait disturbance for the previous 6 days. He had no history of previous illness, drug abuse, or blood transfusion.

On physical examination, the patient was alert and superficial lymphadenopathy and hepatosplenomegaly were not observed. No crackles were heard in the lungs. Erythema was observed on the back of the right hand and forearm. His speech was slow and slurred, but bulbar palsy was not demonstrated. Barre’s leg sign was bilaterally positive.

Laboratory data at the admission were as follows. The leucocyte count was 34,400/mm³, with 35% atypical lymphocytes showing convoluted nuclei, hemoglobin was 13.4 g/dl, and platelet count 120,000/mm³. The serum lactate dehydrogenase level was 2,230 IU/l, glutamic oxaloacetic transaminase 84 IU/l, glutamic pyruvic transaminase 75 IU/l, creatinine 1.2 mg/dl, blood urea nitrogen 35 mg/dl, uric acid 11.8 mg/dl, calcium 16.8 mg/dl (albumin 3.8 g/dl), and inorganic phosphate 2.8 mg/dl. The serum alkaline phosphatase was normal and an M peak was not evident on electrophoresis of the serum. Serum anti-human T-cell lymphotropic virus type I (HTLV-I)-antibody was positive. The serum C- and M-fragments of parathyroid hormone (PTH), intact PTH and calcitonin were all within normal ranges, but parathyroid hormone-related protein (PTHrP) was as high as 503 pg/ml (normal range 109–141). Serum interleukin-1α and -1β were both within normal limits. The surface markers of atypical lymphocytes in the peripheral blood revealed CD3(+) 4(+) 6(-) 8(-) 11(+) 27. The myelogram showed a nucleated cell count of 171,500/mm³ with 15% atypical lymphocytes with convoluted nuclei. Such atypical lymphocytes were also found in the cerebrospinal fluid, and histo-
logical examination of skin biopsy specimens revealed infiltration of atypical lymphocytes, which were T-cell surface marker positive. The brain computed tomogram was normal, but abdominal computed tomogram revealed swelling of the paraaortic lymph nodes and a tiny calcification in the right liver lobe. The electrocardiogram and chest roentgenogram showed no abnormality, but arterial blood gas analysis revealed a pH of 7.49, oxygen tension as low as 53.2 Torr, carbon dioxide tension of 35.6 Torr and base excess of 4.8 mEq/l.

A diagnosis of ATL (acute type) was made, and the presenting symptoms appeared to be caused by hypercalcemia. High-volume hydration with isotonic saline (3,000–7,000 ml/day), loop diuresis, and injection of elcatonin (80–240 units/day) were promptly carried out for the hypercalcemia. Anti-leukemic chemotherapy (consisting of vincristine, cyclophosphamide, prednisolone, doxorubicin and methotrexate) with supportive therapy was also started with oxygen inhalation. However, the treatments for hypercalcemia were ineffective. The laboratory data on the 8th hospital day showed serum creatinine 2.4 mg/dl, blood urea nitrogen 74 mg/dl, calcium 17.2 mg/dl (albumin 2.5 g/dl) and inorganic phosphate 6.9 mg/dl. Arterial blood gas analysis revealed a pH of 7.51, oxygen tension of 74.5 Torr, carbon dioxide tension of 32.0 Torr, bicarbonate of 25.6 mEq/l and base excess of 4.2 mEq/l while breathing 50% oxygen by a face mask. Hemodialysis was started and the laboratory data were improved on the 14th hospital day; the leukocyte count was 4,500/mm³, with 3% atypical lymphocytes, serum calcium was 10.7 mg/dl (albumin 2.7 g/dl), inorganic phosphate 3.4 mg/dl, and serum lactate dehydrogenase 772 IU/l. However, on the chest roentgenogram, an infiltrative-like shadow appeared in the left lung and extended throughout both lungs (Fig. 1) with the progression of neutropenia (Fig. 2). Cardiac enlargement was not observed on the chest roentgenogram, central venous pressure was less than 10 cm H₂O, and an ultrasonic cardiogram revealed neither left ventricular dilatation nor pericardial effusion. The results of sputum smear and culture were negative, and broad-spectrum antibiotics, antimycobacterial agents, antifungal agents and trimethoprim-sulfamethoxazole were all ineffective. Due to progressive respiratory insufficiency, he died 32 days after admission.

At autopsy, microscopic examination revealed infiltration of ATL cells in almost all organs, including liver, spleen, pancreas, bladder, lungs, pericardium, and meninx, as well as peripancreatic, retroperitoneal and hilar lymph nodes. Moreover, there were metastatic calcifications in the lungs, heart, liver, spleen, kidneys, urinary bladder, meninx and other organs. The calcifications were most marked in both lungs, along the alveolar septae and much more remarkable than infiltration of ATL cells (Fig. 3); there were few calcifications in the left upper lobe, where no infiltrative-like shadow appeared on the chest roentgenogram. No evidence of pneumonia caused by infection was found. Along the bone trabeculae, osteoclasts increased conspicuously. Neither hyperplasia nor adenoma of the parathyroid glands was observed.

Discussion

Metastatic calcification is associated with abnormal calcium metabolism and is often observed in various malignancies associated with hypercalcemia and in chronic renal failure with secondary hyperparathyroidism (1–9). Although the frequent occurrence of hypercalcemia has been shown to be one of the most remarkable characteristics, metastatic calcification in the lungs is not common in the patients with ATL (10–19). The present case involved ATL with severe hypercalcemia, complicated by respiratory insufficiency due to metastatic calcification in the lungs.

Hypercalcemia has been reported to be a common complication of ATL, with an incidence of 40% to 70% (10–15, 20). At autopsy, proliferation of osteoclasts with extensive bone resorption has been observed in cases with ATL (21). This hypercalcemia was closely associated with elevated nephrogenous cyclic adenosine monophosphate and reduced serum 1, 25-dihydroxyvitamin D₃ concentration with a low to normal immunoreactive PTH level (20). The humoral factor, PTHrP produced by tumor cells in ATL, is believed to play an important role in the development of hypercalcemia by stimulating osteoclastic bone resorption (9, 15, 18, 22–25). PTHrP gene expression in HTLV-I infected T cells has been reportedly induced through transactivation by the tax gene in vitro (26). Moreover, hypercalcemia may be provoked by other factors such as the number of tumor cells and the presence of some
additional substances such as interleukin-1α, 1β, 2 and prostaglandin E, (27–33). In the present case, the elevated serum PTHrP level was probably involved mainly in the mechanism of hypercalcemia.

The lung is the most frequent visceral site of metastatic calcification (4, 5). Deposition occurs in the alveolar septae and/or the alveolar space. The other visceral organs usually involved are kidneys, stomach and heart (2, 4, 13). The most important factor in the deposition of calcium salts is the supersaturation of extracellular fluid with calcium and phosphate ions. A plasma calcium-phosphate ion product excess of 70 is the level at which calcium is precipitated (4). Moreover, formation of metastatic calcification depends on the systemic and local tissue pH. Three of the most involved sites, i.e., the alveolar septae of the lungs, the renal tubular epithelium and the gastric mucosa, are associated with the secretion of free hydrogen ions, and tend to be more alkaline where calcium is preferentially deposited (3–9, 13). In this case, both serum calcium and phosphate levels were increased and metabolic alkalosis were observed on the laboratory data when the abnormal shadow appeared in patient’s lung. In addition, worsening renal insufficiency superimposed on abnormalities in calcium and phosphate metabolism could
calcifications were much more remarkable than the infiltration chest shadow appeared and became extended. Moreover, the leukemic chemotherapy, during the period when the abnormal lymphocytes in the peripheral blood were decreased by anti-

in the lungs. The leukocyte count was improved and atypical revealed metastatic calcification and infiltration of ATL cells (2-4). This case presented respiratory insufficiency without and atypical chest shadow. More extensive studies of various humoral factors accounting for hypercalcemia in ATL are required to reverse the course of this potentially lethal complication and to improve the prognosis.

Aggressive management of hypercalcemia using 0.9% saline together with two kinds of osteoclast inhibitors, calcitonin and biphosphonate, should be instituted early to avoid fatal metastatic calcification. Gallium nitrate, another potent osteoclast inhibitor, may be used if biphosphonate therapy is unsuccessful. The somatostatin analog octreotide has been shown to be effective in the treatment of hypercalcemia of malignancy due to secretion of PTHrP (36). The biphosphonate was not available commercially when our patient had treatments.

Although pulmonary calcification is generally slowly progressive and often asymptomatic, there have been several reports of acute respiratory insufficiency with a rapidly progressive chest shadow that mimics pneumonia or pulmonary edema (2-4). This case presented respiratory insufficiency without signs of heart failure, and the chest roentgenogram was suggestive of pneumonic infiltration accompanied by the progression of neutropenia. We considered this chest shadow to represent pulmonary infection. However, postmortem examination revealed metastatic calcification and infiltration of ATL cells in the lungs. The leukocyte count was improved and atypical lymphocytes in the peripheral blood were decreased by antileukemic chemotherapy, during the period when the abnormal chest shadow appeared and became extended. Moreover, the calcifications were much more remarkable than the infiltration of ATL cells in the alveolar septae. Therefore, the cause of the abnormal chest shadow was considered not to be infiltration of tumor cells, but rather the metastatic calcification in the lungs. This extensive calcification in alveolar septae reduced the diffusion capacity and resulted in severe alveolar-capillary block that led to the initial respiratory insufficiency. Although, in this case, the chest roentgenogram showed no abnormalities on admission, the arterial oxygen tension was decreased. This fact suggests that metastatic calcification in the lungs had already occurred before the development of the abnormal chest shadow. To avoid the progression of respiratory failure in patients with ATL and hypercalcemia, it is important to suspect that hypoxemia in the absence of an abnormal chest shadow may result from early metastatic pulmonary calcification, and to perform bone scintigraphy for early detection of such calcification.

The present case suggests that the possibility of metastatic calcification in the lungs should always be considered in patients with ATL associated with hypercalcemia when respiratory insufficiency is observed, with or without an abnormal chest shadow. More extensive studies of various humoral factors accounting for hypercalcemia in ATL are required to reverse the course of this potentially lethal complication and to improve the prognosis.

References


Figure 3. Microscopic findings of the lung showed diffuse septal calcification (HE stain, x33).
in English).


