

Case Report

Acute Respiratory Distress Syndrome Associated with Hypercalcemia without Parathyroid Disorders

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Abstract

Acute lung injury (ALI) can be induced by various causes. The occurrence of ALI associated with hypercalcemia has rarely been reported and the mechanisms are unknown. In the present study, we reported the clinical manifestation and pathological findings in patients with hypercalcemia and metastatic calcification. In addition, we addressed the possible mechanism and the preventive strategy for the acute episode of ALI due to hypercalcemic crisis. We encountered five patients with long-term malignancy of various origins. They displayed hypercalcemia and metastatic calcification in the kidney and stomach. One case with transitional cell carcinoma of the urinary bladder developed acute episode of acute respiratory distress syndrome (ARDS). The plasma calcium was elevated to above 5 mM. Simultaneously, He manifested ARDS followed by ALI. The pathological examination revealed severe alveolar edema with multiple calcification. In the other three cases, the plasma calcium level ranged from 3.1 to 4.4 mM and ARDS or ALI did not occur. One patient with esophageal squamous cell carcinoma experienced an acute hypercalcemia (plasma calcium 4.8-5.1 mM) accompanied by ARDS. Corticosteroid and calcitonin were prescribed to reduce the plasma calcium. The symptoms of ARDS also subsided and ALI did not occur. Chronic hypercalcemia results in severe metastatic calcification. The kidney and stomach are the most vulnerable organs. An increase in plasma calcium above 5 mM is a risk factor for developing ARDS and ALI. Our recent experiment in conscious rats and isolated rat's lungs supported this contention. In addition, corticosteroid and calcitonin were able to reduce the plasma calcium and to prevent the occurrence of ARDS and ALI.

Key Words: acute respiratory distress syndrome, acute lung injury, hypercalcemia, calcification, alveolar hemorrhage, nephrocalcinosis

Introduction

Fulminant acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) can be induced by a variety of disorders (3-9, 14-18, 21, 24). We first reported the neural mechanism of neurogenic ALI caused by cerebral compression (7). The hemodynamic changes underlying the centrogenic ALI were elucidated to be that central sympathetic activation caused blood

volume shift from the systemic circulation to the lung (5, 6, 21). Recent clinical investigations from our research group reported acute ALI caused by Japanese B encephalitis, EV 71, fat embolism and other disorders (4, 14, 17, 18). The mechanisms involve central sympathetic activation causing volume and pressure loading in pulmonary circulation and are similar to the neurogenic ALI following brain injury (3, 6).

In a total of 217 autopsy cases, we encountered

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Table 1. Patients with metastatic calcification in various organs due to different disease origin and the plasma concentration of calcium and phosphorus

Case	Sex	Age	Disease and Origin	Calcium (mM)	Phosphorus (mM)	Organ Involvement
Death with ARDS	male	37	Transitional cell carcinoma in the urinary bladder	5.3-5.9	2.4-3.2	lung, kidney, stomach, salivary glands and pancreatic duct
Death without ARDS	male	63	Multiple myeloma	3.8-4.1	1.6-1.8	kidney, stomach and heart
	male	49	Squamous cell carcinoma in the esophagus	4.2-4.4	2.4-3.8	kidney, stomach and heart
	male	83	Small cell carcinoma in the lung with multiple bone metastasis	3.1-3.5	2.2-3.6	kidney and stomach
	male	48	Squamous cell carcinoma in the esophagus	*4.8-5.1 → 3.4-3.8	*3.4-3.8 → 2.8-3.2	kidney and stomach

Note: ARDS = acute respiratory distress syndrome. The five cases are classified into death with and without ARDS.

* In this case, corticosteroid and calcitonin are administered. The values before and after the arrow indicate the plasma calcium and phosphorus levels prior to and following treatment.

five cases with severe hypercalcemia followed by metastatic calcification. Holmes *et al.* reported a case with hypercalcemic crisis resulting from parathyroid adenoma of the chief cells (13). In this case, the plasma calcium level is 25 mg/ml (5.8 mM), more than twice the normal range (2.1-2.6 mM). The patient finally developed respiratory stress and died of acute lung injury which was later proved by pathological findings upon autopsy. Herein, we reported five cases of hypercalcemia without evidence of parathyroid disorders. One patient died of ARDS following an acute episode of hypercalcemic crisis. Upon autopsy, severe ALI with calcium depositions in the lung and nephrosclerosis in the kidney were found. We compared the clinical manifestations and progression of calcium concentration changes with the other four mortality cases died of other causes without overt respiratory distress before death. This report may provide information to the clinicians that plasma calcium level may be a high risk factor in diseases other than parathyroid adenoma. In such cases, death may ensue, if appropriate treatment is not given.

Materials and Methods

Patients, Case Classification and Basic Data

From 2001 to 2006, the hospital had a total of 217 autopsy cases. We encountered five with metastatic calcification. One patient died of an acute episode of respiratory distress following hypercalcemic crisis.

Table 1 summarizes the sex, age, disease origin,

plasma calcium and phosphorus concentration, and organ involvement. The age ranged from 37 to 83. The patient who died of ARDS was a young man with transitional cell carcinoma in the urinary bladder. The other four cases suffered from cancers such as multiple myeloma, squamous cell carcinoma in the esophagus and small cell carcinoma in the lung with multiple bone metastasis.

Laboratory and Pathological Examinations

The plasma calcium and phosphorus concentrations were determined by the hospital Laboratory Division. Consent for autopsy was obtained from the patients before expiry or from their relatives. The lung, kidney, esophagus, stomach, salivary glands, parathyroid glands, and other organs were taken for examination. The organs were cut into small pieces and immersed in 10% paraformaldehyde. The tissue specimens were then dehydrated and embedded in paraffin. The paraffin blocks were sectioned at a thickness of 5 μ m and stained with hematoxylin and eosin. The histopathological examination was performed with a light microscope.

Results

Progression of the Disease

The five cases studied had suffered from different cancers of various origins including transitional cell carcinoma in the urinary bladder, multiple myeloma, squamous cell carcinoma in the esophagus and small

cell carcinoma in the lung with multiple bone metastasis (Table 1). On admission, these patients appeared lethargic and emaciated with chief complaints of fatigue, irritability, malaise, and anorexia. Nausea and vomiting occurred occasionally in some cases. One young man with transitional carcinoma in the urinary bladder received installation of a cystostomy tube to facilitate urinary passage. At the same time, a needle biopsy of the tumor was undertaken for pathological examination. Evaluation of the consciousness with Glasgow Coma Scale (GCS) revealed a level of E₄ V₄ M₃ on admission. The GCS was gradually declined to E₂ V₁ M₁ and E₁ V₁ M₁ at 6 days after admission. Two days later, a severe increase in plasma calcium concentration to 5.3-5.9 mM occurred with increase in phosphorus, sodium, and potassium. In addition, azotemia, thrombocytopenia and urinary tract infections occurred. The patient's symptoms were uncontrollable with general procedures and the clinical conditions progressively worsened. He was announced expired 8 days after admission.

The other four cases with hypercalcemia died within 10 to 26 days after admission. Before death, we only noticed mild respiratory distress. One case, aged 48 years with esophagus squamous cell carcinoma, developed severe hypercalcemia (4.8 to 5.1 mM) and respiratory distress at eight days after admission. Corticosteroid (prednisolone, 1 mg/kg) and calcitonin (4 unit/kg) were prescribed due to the possible occurrence of ALI. The plasma calcium concentration was soon reduced to 3.4-3.8 mM (Table 1) and the respiratory distress syndrome was controlled. This patient eventually expired due to sepsis 26 days after admission. The other three patients died of multiple organ failure after chronic malignancy and metastatic calcification.

Autopsy Findings

All patients were cachexic. The patient died of ARDS had a large bladder tumor measuring 22 × 19 cm that had almost replaced the entire bladder cavity. On serial sections, the tumor had directly invaded into the abdominal wall. On an average, the lung weight remarkably increased (right: 1104 gm and left 899 gm) over the normal value of unilateral lung (350-400 gm). Histopathological examination found severe alveolar hemorrhagic edema in the lung (Fig. 1, A and B). In all cases, metastatic calcification involved renal tubule resulting in severe nephrocalcinosis (Fig. 2A), calcium deposition in the stomach, salivary glands (Fig. 2, B and C) and pancreatic ducts was the common pathological feature (Table 1). We carefully examined the parathyroid glands and did not find hyperplastic lesions and adenomatous changes. The carcinoma in various organs has been confirmed histopathologically (Table 1).

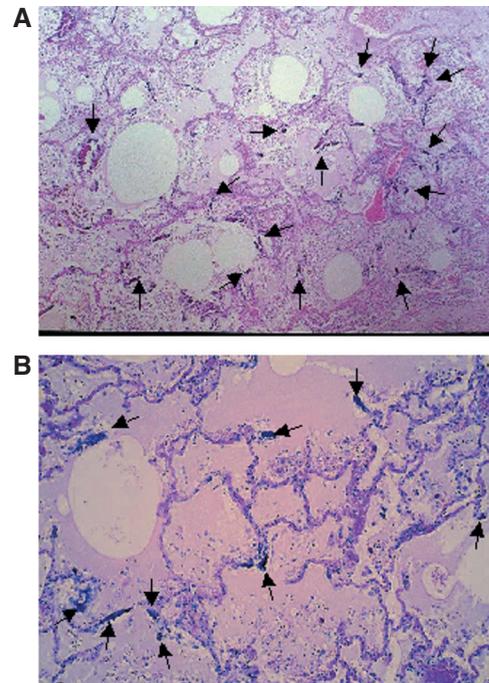


Fig. 1. Acute alveolar hemorrhagic edema with multiple calcium deposition (arrows) in a case died of acute respiratory distress syndrome. Hematoxylin and eosin stain, original magnification ×100 (A) and ×200 (B).

Discussion

The causes of hypercalcemia include hyperparathyroidism, multiple bone metastasis, paraneoplastic syndrome, sarcoidosis, vitamin D intoxication, and decreased renal excretion of calcium. Transitional cell carcinoma associated with hypercalcemia is not common (19). Our findings suggested that long-term hypercalcemia resulted in metastatic calcification in many organs. In addition, we found that the lungs, kidney and stomach are the most vulnerable target organs for calcium deposition (Table 1). Virchow has suggested that the organs excreting acid are slightly alkaline and have a high affinity to bind with calcium (23). Most likely, this is the reason calcium depositions develop in the lung, kidney and stomach following long-term hypercalcemia.

Holmes *et al.* first reported that a case with hypercalcemia crisis died of acute pulmonary edema (13). Calcium deposition in the alveolar epithelial or endothelial cells may destroy the alveolar-epithelial-endothelial barrier to cause acute lung injury. They also found that the plasma calcium level was close to 6 mM with a slight increase in phosphorus concentration. In the present report, the patient died of ARDS displayed a marked high calcium level (5.3-5.9 mM) and high phosphorus. It appeared that a plasma calcium level

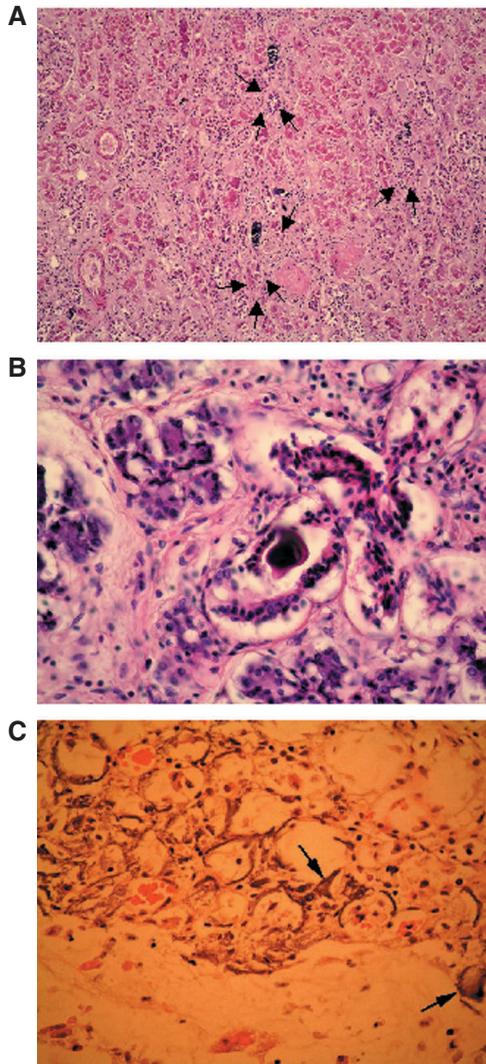


Fig. 2. Severe nephrocalcinosis (A, arrows), and calcium deposition in the salivary gland (B) and stomach (C). The black color indicates deposits of calcium. Hematoxylin an eosin stain, original magnification $\times 200$.

close to or above 5 mM is a risk factor for developing acute lung injury. This contention was supported by a recent experimental study from our laboratory (8). In conscious rats and isolated perfused rat's lungs, an increase in calcium concentration from 2.3 to 5.3 mM produced severe acute lung injury. We also revealed that hypercalcemia increases nitrate/nitrite, methyl guanidine, tumor necrosis factor $_{\alpha}$, interleukin-1 $_{\beta}$, and procalcitonin in plasma and lung perfusate. In addition, hypercalcemia upregulated the inducible NO synthase (iNOS) mRNA expression in the lung parenchyma and iNOS activity in the alveolar macrophage and epithelial cells. The hypercalcemia-induced acute lung injury and associated changes were attenuated by pretreatment with calcitonin and L-N⁶(1-iminoethyl)-lysine (an iNOS inhibitor). The animal experimentations not only advocate

that hypercalcemia is detrimental to the lung, but also elucidate the possible mechanisms involved in the ALI caused by hypercalcemia.

In one case with esophageal squamous cell carcinoma, the plasma calcium was once increased to 5.1 mM and acute respiratory distress syndrome simultaneously appeared. The ARDS subsided after reducing calcium levels to 3.4-3.8 mM by administrating corticosteroid (prednisolone) and calcitonin. These findings provide information to clinicians that the control of calcium concentration may be essential for preventing acute lung injury.

In the present report, there were two cases with esophageal carcinoma (Table 1). Geddes *et al.* found that hypercalcemia was associated with squamous cell carcinoma of the esophagus with a rate of 27.6% (12). Interestingly, transitional cell carcinoma of the urinary bladder may produce a parathyroid hormone-related protein (PTHrP) (2). The PTHrP may act as a parathyroid hormone thus causing hypercalcemia. In addition, increases in PTHrP and/or cytokines in malignancy may stimulate bone osteolysis and inhibit bone resorption as well as tubular calcium reabsorption leading to hypercalcemia (11). Accordingly, the effects of PTHrP and/or cytokine on the hypercalcemia-induced acute lung injury is a subject for future investigation.

Calcium ion plays an important role in normal physiological functions and works as a messenger in cell signal transduction (1, 10, 20). Hypercalcemia, however, may be detrimental to the organs including the lung. It has been shown that an increase in intracellular calcium concentration activates transient receptor potential gene family of channels that encode functional store-operated cation channels. High calcium also initiates endothelial cell contraction and increases endothelial permeability. The mechanism is likely mediated through endothelial cells signaling *via* the nuclear factor- κ B (22).

Our laboratory data also revealed that the plasma phosphorous concentration was moderately elevated (Table 1). The association of calcium and phosphorus metabolism has been well established. PTHrP, cytokines and/or impaired renal excretory function may be attributable, at least in part, to the high calcium and phosphorus levels. Holmes *et al.* (13) speculated that high calcium-phosphorus products led to metastatic calcification. In their data and the data of this study, the increase in phosphorus level was not as marked as the increase in calcium. The role of phosphorus in the genesis of metastatic calcification requires further investigation.

In conclusion, we reported five cases with hypercalcemia following chronic malignancy of various types in different organs. One patient died of an acute episode of hypercalcemia crisis and acute ARDS. Metastatic calcification developed in the kidney and

stomach in all patients. Corticosteroid and calcitonin were used in one case with hypercalcemic crisis and respiratory distress. The treatment reduced calcium concentration and prevents the occurrence of ARDS. Acute and chronic administration of the calcium lowering agents may be a potential therapeutic choice for hypercalcemia with metastatic calcification and respiratory distress. A recent experimental study from our laboratory using conscious rat model and isolated rat's lungs supports the detrimental role of hypercalcemia and elucidate the possible mechanisms of hypercalcemia-induced ALI (data not shown).

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