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Case report

A rare case of parathyroid crisis with respiratory failure successfully treated using extracorporeal membrane oxygenation

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ABSTRACT

Parathyroid crisis, which might occur during the natural history of primary hyperparathyroidism, presents fatal hypercalcemia. Although hyperparathyroidism is known to cause metastatic pulmonary calcification, parathyroid crisis with respiratory failure is rarely reported. Here, we present a case of parathyroid crisis with respiratory failure due to parathyroid adenoma. For the first 2 weeks after admission to our hospital, the patient was treated with hydration, calcium-lowering agents, dialysis and extracorporeal membrane oxygenation, with gradual improvement in her respiratory condition as blood calcium levels decreased. However, she still needed oxygen even after that. Therefore, parathyroidectomy was performed on day 48, and she no longer needed oxygen after the surgery. Chest computed tomography scan also demonstrated improvement in pulmonary calcification, although it did not completely disappear even 4 months after parathyroidectomy. Parathyroid crisis is an endocrine emergency, and its possibility should be considered in patients with respiratory failure with hypercalcemia.

1. Introduction

Primary hyperparathyroidism (PH) is a disease characterized by hypercalcemia due to oversecretion of parathyroid hormone (PTH) by parathyroid adenoma, hyperplasia or tumor [1,2]; it typically has a chronic course. While most patients with PH are asymptomatic [3], rapid hypercalcemia can occur, causing dehydration and multiple organ dysfunction, including gastrointestinal, renal, neurological and cardiovascular problems [2–4]. This rare and potentially fatal condition is called parathyroid crisis, also known as parathyroid storm or hypercalcemic crisis [3,5].

On the other hand, PH with respiratory tract symptoms is rare [1]. In a few previous papers, patients with PH were reported to have metastatic pulmonary calcification (MPC), a condition which involves calcium deposition in the normal lung [1,6,7]. However, parathyroid crisis with acute respiratory failure has seldom been reported before. We herein present a case of parathyroid crisis with acute respiratory failure. Due to its rarity, acute development of respiratory failure due to parathyroid crisis is easily misdiagnosed as bacterial or interstitial pneumonia. Our experience suggests that parathyroid crisis should be considered in the differential diagnosis of respiratory failure, particularly in cases with concurrent hypercalcemia. We present and discuss the detailed clinical course of this case with reference to previous reports.

2. Case report

The patient was a 46-year-old woman with a history of long-term schizophrenia. She had no other notable medical history and no history of smoking. Just before being brought to our hospital, she had been in a psychiatric hospital for one month because of her unstable mental condition due to schizophrenia. She developed a non-productive cough one week before admission to our hospital, and was admitted to the intensive care unit (ICU) due to dyspnea. Physical examination revealed the following results: Glasgow Coma Scale score E4V4M6, body temperature 36.5 °C, pulse 94 beats/min, and blood pressure 88/64 mmHg. Arterial blood gas analysis indicated severe hypoxia even while breathing 8 L/min of oxygen via an oxygen mask (pH 7.420, PaO_2 48.1 torr, $PaCO_2$ 48.5 torr, HCO_3^- 30.9 mmol/L). Additionally, her corrected serum calcium level was elevated (15.2 mg/dL). The results of her blood tests are shown in Table 1. Chest X-ray showed bilateral infiltrates

Abbreviations: CHDF, continuous hemodiafiltration; CT, computed tomography; ICU, intensive care unit; MPC, metastatic pulmonary calcification; PH, primary hyperparathyroidism; PTH, parathyroid hormone; VV-ECMO, veno-venous extracorporeal membrane oxygenation.

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(Fig. 1) and chest computed tomography (CT) revealed bilateral ground-glass opacities (Fig. 2). Urine antigen test for Legionella, sputum LAMP assay for Mycoplasma, serologic tests for HIV, HTLV-1 and serum beta-D-glucan were all negative. Echocardiography showed normal left ventricular systolic function. She was intubated on the day of admission.

Considering the possibility of bacterial pneumonia, antibiotic therapy was initiated. However, cultures of sputum, blood, and bronchoalveolar lavage fluid were negative. Regarding bronchoalveolar lavage fluid, total cell count was 5.0×10^5/ml, and neutrophils were predominant (neutrophils 63%, lymphocytes 19%, macrophages 17%, eosinophils 1%). To treat renal failure due to dehydration, aggressive saline infusion was started. Moreover, calcitonin and bisphosphonates (zoledronic acid) were also administered for hypercalcemia, although its etiology was still unknown. However, even after intubation, arterial blood gas analysis showed sever hypoxia and hypercapnia (pH 7.110, PaO_2 51.4 torr, $PaCO_2$ 85.6 torr, HCO_3^- 20.9 mmol/L) on pressure control mode of ventilation with the following setting: FiO2 0.8, respiratory rate 30 breaths/min, pressure control 18 cmH_2O, positive end expiratory pressure 12 cmH_2O. On day 2, it became no longer possible to maintain oxygenation with usual invasive mechanical ventilation, hence veno-venous extracorporeal membrane oxygenation (VV-ECMO) was initiated. On day 3, continuous hemodiafiltration (CHDF) was initiated to correct fluid overload and serum calcium levels. From day 4, steroid therapy was started considering the possibility of interstitial pneumonia. During these treatments, her respiratory condition and hypercalcemia gradually improved, and she was disconnected from ECMO on day 6 and extubated on day 7. She was discharged from the ICU on day 8, following which further therapy was continued in a psychiatric ward at our hospital. Antibiotic therapy was stopped on day 14, and the steroid dose was gradually tapered. Her clinical course for the first 14 days after admission is shown in Fig. 3. Although her respiratory condition did not deteriorate again, she still needed 1 L/min of oxygen even after the first 2 weeks of treatment.

Evaluation revealed that intact PTH levels on the day of admission were extremely high (3463.3 pg/mL) and CT image on the day of admission showed swelling of her left parathyroid gland (Fig. 4). Moreover, the results of parathyroid scintigraphy were consistent with parathyroid tumor (Fig. 5). Follow-up chest CT scan showed calcification in both lungs (Fig. 6C–F), and Tc-99m hydroxymethylene diphosphonate scintigraphy also showed diffuse uptake in both lungs (Fig. 7). Finally, transbronchial lung biopsy obtained on day 47 revealed microscopic calcification in small vessel walls, which is consistent with MPC (Fig. 8).

Based on the above results, parathyroidectomy was performed on day 48, the pathological findings of which were consistent with parathyroid adenoma (Fig. 8). Two weeks after surgery, she no longer needed oxygen therapy. Four months after surgery, follow-up CT scan revealed improvement in pulmonary calcification bilaterally (Fig. 6G and H).

Table 1
Laboratory data on admission.

Hematology			γ-GTP	26	U/L
WBC	21,700	/μL	LHD	328	U/L
Neutrophil	94.3	%	CK	109	U/L
Lymphocyte	4.2	%	BUN	77.2	md/dL
RBC	280×10^4	/μL	Cr	4.89	mg/dL
Hb	8.4	g/dL	Na	130	mmol/L
Plt	27.7×10^4	/μL	K	2.5	mmol/L
			Cl	88	mmol/L
Biochemistry			Ca	13.6	mg/dL
TP	5.0	g/dL	Corrected Ca	15.2	mg/dL
Alb	2.4	g/dL	P	4.7	mg/dL
T-bil	0.3	mg/dL	BNP	135	pg/mL
AST	38	U/L			
ALT	32	U/L	Serology		
ALP	691	U/L	CRP	27.63	mg/dL
			Coagulation		
			PT%	72.3	%
			APTT	29	sec

Alb: albumin, ALP: alkaline phosphatase, ALT: aspartate aminotransferase, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BNP: brain natriuretic peptide, BUN: blood urea nitrogen, Ca: calcium, CK: creatine kinase, Cl: chloride, Cr: creatinine, CRP: C-reactive protein, γ-GTP: gamma-glutamyl transpeptidase, Hb: hemoglobin, K: potassium, LDH: lactate dehydrogenase, Na: sodium, P: phosphorus, Plt: platelet, PT: prothrombin time, RBC: red blood cell, T-bil: total bilirubin, TP: total protein, WBC: white blood cell.

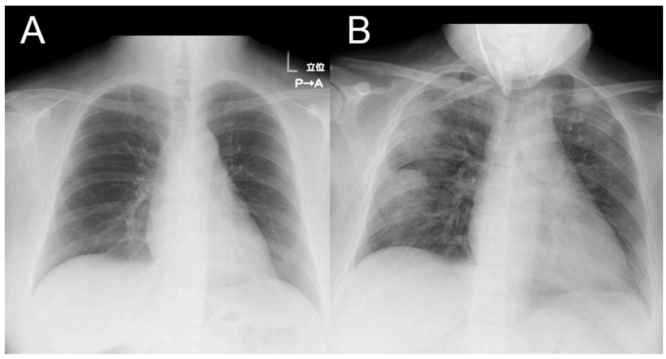

Fig. 1. Chest-X-ray. (A) One month prior to admission to our hospital, there were no abnormal chest shadows. (B) New bilateral infiltrates were detected on the day of admission.

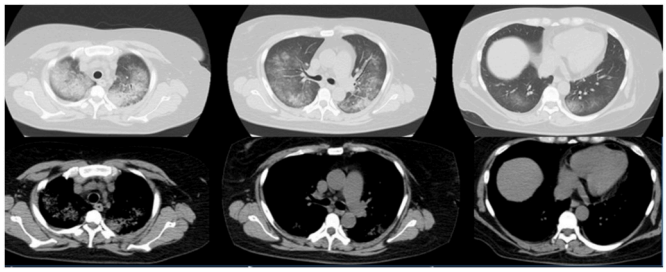

Fig. 2. Chest computed tomography on the day of admission. Bilateral ground-grass opacities were detected, while pulmonary calcification was not clearly detected.

3. Discussion

We present here a rare case of respiratory failure due to parathyroid crisis that was successfully treated using VV-ECMO. Parathyroid crisis, also known as parathyroid storm or hypercalcemic crisis, is a fatal endocrine emergency that could occur at any point during the natural history of PH [3,5]. It usually evolves from preexisting modest hypercalcemia into an acute hypercalcemic exacerbation, and can impact various organ systems [3]. A previous paper reported that both blood calcium levels no less than 13.25 mg/dL and PTH levels no less than 394 pg/mL were risk factors for parathyroid crisis [8]; blood levels of calcium and PTH were 15.2 mg/dL and 3463.3 pg/mL, respectively, in our patient. The extremely high intact PTH level probably caused the parathyroid crisis.

The patient's respiratory condition gradually improved as her blood calcium and creatinine levels decreased during treatment (Fig. 3). In this case, it is likely that acute respiratory failure was mainly caused by renal failure due to hypercalcemia. We also think that aggressive saline infusion for treating renal failure and hypercalcemia exacerbated pulmonary edema. On the other hand, in a previous paper, Chen et al. reported that hypercalcemia might cause pulmonary edema by increasing the activity of inducible nitric oxide synthase in alveolar macrophages

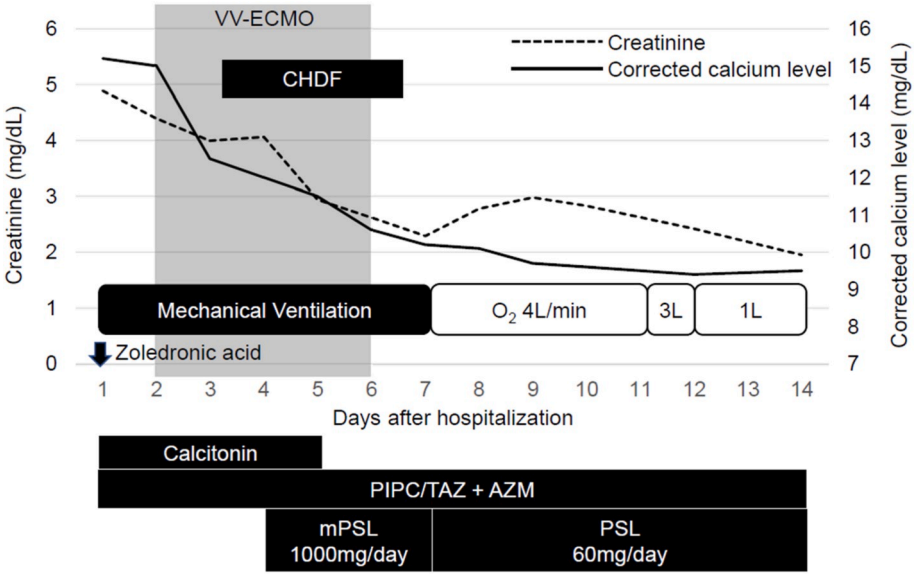

Fig. 3. The clinical course of the patient.
AZM: azithromycin, CHDF: continuous hemodiafiltration, mPSL: methylprednisolone, PIPC/TAZ: piperacillin/tazobactam, PSL: prednisolone, VV-ECMO: veno-venous extracorporeal membrane oxygenation.

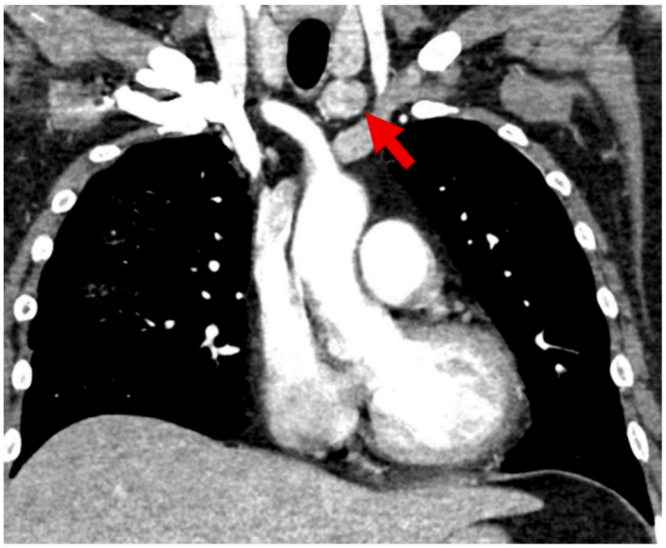

Fig. 4. Computed tomography finding of the left parathyroid grand. Swelling of the parathyroid grand was detected (arrow).

and epithelial cells [9]. Since hypercalcemia-induced pulmonary edema can be reversed by treating hypercalcemia, as seen in this case, treatment with ECMO is a good option when usual invasive mechanical ventilation cannot maintain the patient's oxygenation.

Moreover, in this patient, transbronchial lung biopsy showed calcium deposition in the lung, which was consistent with MPC. Usually, MPC develops over a long period of time, mainly in patients with hyperparathyroidism secondary to chronic renal failure, and the majority of them are asymptomatic. However, in a few previous reports, acute development of MPC due to PH caused respiratory failure and even death [6,10]. MPC is considered to cause respiratory failure when calcification lowers lung compliance and diffusion capacity to some threshold level [6]. Actually, this patient still needed 1 L/min of oxygen even after correcting blood calcium level. Hence, we believe that development of MPC was also the cause of respiratory failure in this case.

MPC is usually difficult to diagnose in its early phase, even by chest CT scan, and is easily misdiagnosed as other pulmonary diseases [7]. In our case, pulmonary calcification was not clearly detected by chest CT scan on the day of admission, and it only appeared gradually during treatment (Fig. 6). When acute development of MPC is suspected, Tc-99m hydroxymethylene diphosphonate scintigraphy or lung biopsy should be performed to differentiate MPC from other diseases [7]. Also, resolution of pulmonary calcification on chest radiography is usually limited even after lowering blood calcium levels [7]. In this patient, chest CT scan demonstrated improvement in pulmonary calcification, although it did not completely disappear even 4 months after parathyroidectomy (Fig. 6G and H).

There is no established therapy for parathyroid crisis [3]. Early surgical parathyroidectomy is regarded to be the most effective

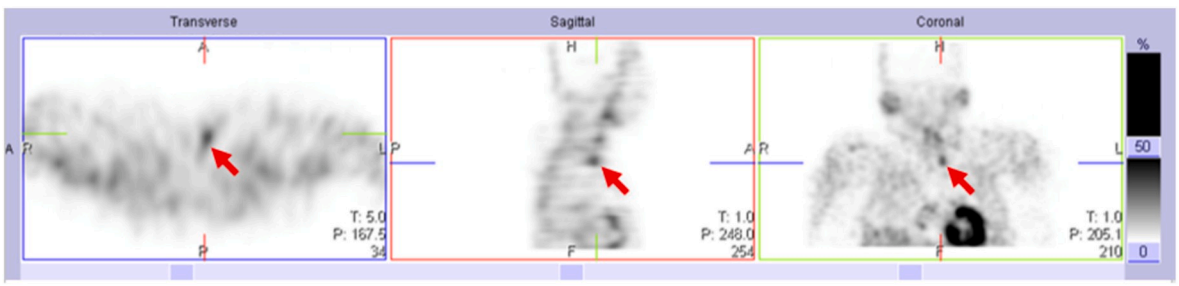

Fig. 5. Parathyroid scintigraphy obtained on day 33 demonstrated a left parathyroid tumor (arrow).

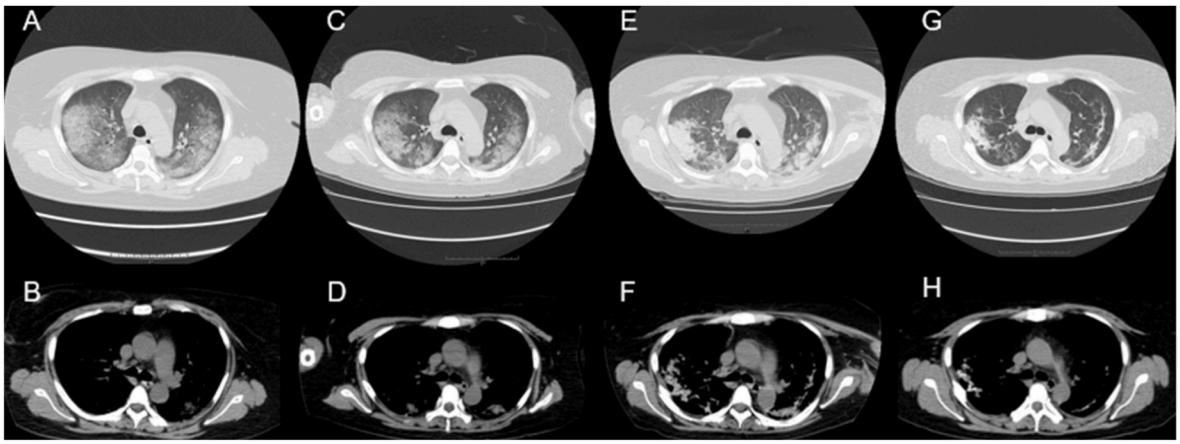

Fig. 6. Chest computed tomography. A and B are images on the day of admission. C and D are images obtained on day 13. E and F are the images of day 45. Follow-up chest CT scans showed calcification in both lungs (C-F). G and H are images obtained 4 months after parathyroidectomy, and they demonstrated improvement in pulmonary calcification.
CT: computed tomography.

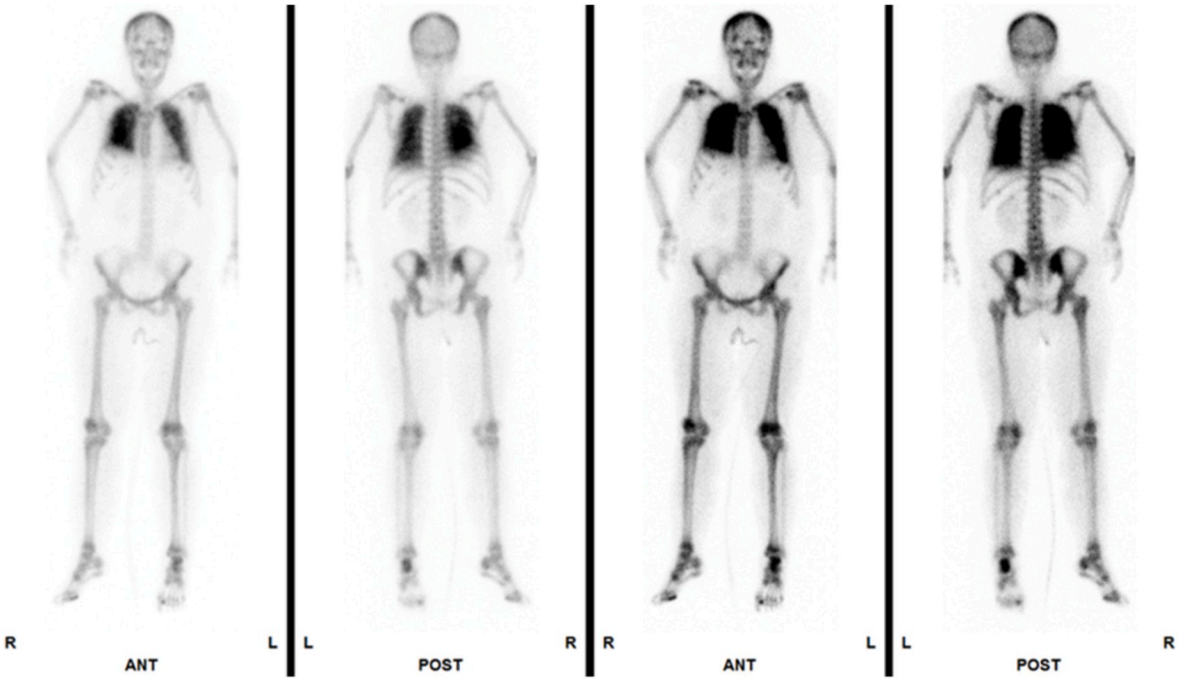

Fig. 7. Tc-99m hydroxymethylene diphosphonate scintigraphy obtained on day 40. Diffuse uptake was detected in both lungs.

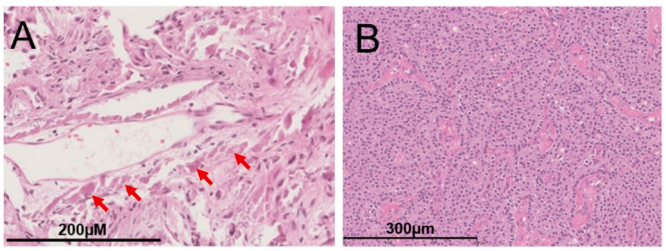

Fig. 8. Hematoxylin and eosin staining of tissue sections obtained by transbronchial lung biopsy (A) and parathyroidectomy (B). Calcification was detected in small vessel walls in the lung biopsy specimen (arrows).

approach for primary hyperparathyroidism [4,5], although surgery was delayed in this case because of the patient's unstable mental condition due to schizophrenia. However, medical management, such as 1) correcting dehydration, 2) lowering calcium levels, and 3) decreasing osteoclast-mediated bone resorption are also important, and these managements are regarded as temporary bridging measures until surgery [3]. The usual management includes saline infusion, administration of loop diuretics, bisphosphonates and calcitonin. Dialysis might also be a salvage therapy when other options have failed [3].

4. Conclusions

Parathyroid crisis is a potentially fatal condition that can present with respiratory failure. Due to its rarity, respiratory failure due to parathyroid crisis is easily misdiagnosed as other pulmonary diseases. Hence, the possibility of parathyroid crisis should be considered in

patients with acute respiratory failure with hypercalcemia. Also, because hypercalcemia-induced pulmonary edema is reversible by lowering blood calcium levels, as seen in this case, treatment with ECMO is a good option if usual mechanical ventilation cannot maintain the patient's oxygenation.

Declaration of competing interest

The authors state that they have no conflict of interest.

Credit authorship contribution statement

Shunkichi Ikegaki: Conceptualization, Investigation, Writing-original draft, Writing-review & editing, Visualization. **Takehiro Otoshi:** Conceptualization, Investigation, Writing-original draft, Writing-review & editing, Visualization. **Tomoyuki Hirai:** Writing-review & editing, Supervision. **Masataka Hirabayashi:** Writing-review & editing, Supervision.

Declaration of competing interest

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