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CASE REPORT

Pulmonary and gastric metastatic calcification due to milk-alkali syndrome: a case report

Keiko Yamagami · Tomomi Nakamura · Masatsugu Kishida · Yusuke Hanioka · Tomoyuki Nakamura · Toshimasa Yamaguchi · Masayoshi Nishijima · Takeshi Inoue · Katsunobu Yoshioka · Masahito Imanishi

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Abstract The incidence of metastatic calcification is influenced by high serum calcium and phosphate concentrations and local physicochemical conditions, such as pH. A high pH accelerates tissue calcification. Patients with milk-alkali syndrome typically present with renal failure, hypercalcemia, and metabolic alkalosis, which are caused by the ingestion of calcium and absorbable alkali. Among patients with impairment of renal function, milk-alkali syndrome is a major cause of hypercalcemia. Long-term use of furosemide will lead to hypokalemia, metabolic alkalosis, and eventually renal failure (i.e., pseudo-Bartter syndrome). Even if the level of calcium ingestion is relatively low, the renal failure caused by long-term furosemide use can readily lead to milk-alkali syndrome. We describe a case of a 45-year-old woman who was admitted with cough and dyspnea and presented with pulmonary and gastric metastatic calcification. She had been taking alfacalcidol and oral alkaline medications such as sodium bicarbonate and calcium carbonate as well as oral furosemide for a long time. The patient was found to have hypercalcemia, chronic renal failure, and metabolic alkalosis, so milk-alkali syndrome was diagnosed. Saline was administered and oral medications were discontinued. Serum creatinine levels subsequently decreased, but pulmonary metastatic calcification was not diminished. In this case, the milk-alkali syndrome that caused the severe metastatic calcification was exacerbated by multiple factors, including oral alkaline medications such as sodium bicarbonate and calcium carbonate. In addition, metabolic alkalosis and renal failure were affected by long-term furosemide use (i.e., pseudo-Bartter syndrome).

K. Yamagami (✉) · T. Nakamura · M. Kishida · Y. Hanioka · T. Nakamura · T. Yamaguchi · M. Imanishi
Department of Internal Medicine, Osaka City General Hospital, 2-13-22 Miyakojima-Hondori, Miyakojimaku, Osaka City, Osaka 534-0021, Japan
e-mail: yamasanz@qb3.so-net.ne.jp

T. Nakamura
e-mail: t_schwarze_katze@yahoo.co.jp

M. Kishida
e-mail: masa-kishida@hospital.city.osaka.jp

Y. Hanioka
e-mail: la_sa_sya@hotmail.com

T. Nakamura
e-mail: tomosquared@yahoo.co.jp

T. Yamaguchi
e-mail: toshimasa1@excite.co.jp

M. Imanishi
e-mail: masachan@msic.med.osaka-cu.ac.jp

K. Yamagami
Department of Diabetes and Endocrinology, Osaka City General Hospital, Osaka, Japan

M. Nishijima
Department of Respiratory Medicine, Osaka City General Hospital, Osaka, Japan
e-mail: masa-nishijima@hospital.city.osaka.jp

T. Inoue
Department of Pathology, Osaka City General Hospital, Osaka, Japan
e-mail: m1657676@msic.med.osaka-cu.ac.jp

K. Yoshioka
Department of Internal Medicine, Shitennoji Hospital, Osaka, Japan
e-mail: kyoshioka@shitennoji-fukushi.jp

Keywords Pulmonary metastatic calcification · Stomach metastatic calcification · Milk-alkali syndrome · Chronic renal failure · Pseudo-Bartter syndrome

Introduction

Metastatic calcification may occur with end-stage renal disease and hyperparathyroidism. The incidence of metastatic calcification is influenced by high serum calcium and phosphate concentrations and local physicochemical conditions, such as pH. An alkaline environment (high pH) will accelerate tissue calcification [1].

Patients with milk-alkali syndrome typically present with renal failure, hypercalcemia, and metabolic alkalosis caused by the ingestion of calcium and absorbable alkali. This syndrome is caused by high intake of milk and sodium bicarbonate, which was used for peptic ulcer treatment before the advent of histamine blockers and proton-pump inhibitors. Recently, use of calcium carbonate and vitamin D has increased among the elderly to prevent increases in osteoporosis. These therapies can lead to the modern type of milk-alkali syndrome, which is a major cause of hypercalcemia among individuals with impaired renal function. While pathological calcinosis of the kidneys is not rare, pulmonary or other tissue metastatic calcification due to milk-alkali syndrome is rare, despite a hypercalcemic state [2, 3].

We report the case of a woman who presented with severe pulmonary and stomach metastatic calcification. She developed renal failure caused by long-term oral furosemide intake (i.e., pseudo-Bartter syndrome), and presented with milk-alkali syndrome caused by sodium bicarbonate, calcium carbonate, vitamin D, and an excessive daily intake of milk. Certain aspects regarding the mechanisms underlying the resulting severe metastatic calcification are discussed.

Case presentation

A 45-year-old woman was admitted to our hospital with a three-month history of severe cough and worsening renal function. She had been diagnosed with chronic renal failure (CRF) several years earlier and her serum creatinine level was 2.99 mg/dl three months before presentation.

She had been taking many drugs, including antidepressants, furosemide (80 mg/day), spironolactone (25 mg/day), potassium L-aspartate (900 mg/day), alfacalcidol (0.25 μg/day), ursodeoxycholic acid (300 mg/day), allopurinol (100 mg/day), rosuvastatin calcium (2.5 mg/day), and an over-the-counter stomach pain medicine containing sodium bicarbonate (900 mg/day), calcium carbonate (1200 mg/day), and magnesium oxide (100 mg/day). She had also been orally ingesting 200 ml of milk and yoghurt daily, amounting to a total of 420 mg of calcium per day. She was not taking thiazide diuretics. Upon examination,

Table 1 Laboratory parameters on admission

Blood count				*Urinalysis*	
White blood cell	15510/mL	Sodium	130 mEq/L	pH	7.0
Neut	74 %	Potassium	3.3 mEq/L	Protein	(±)
Lyp	12 %	Chloride	83 mEq/L	Sugar	(−)
Hb	8.2 g/dL	Calcium	10.6 mg/dL	Blood	(+)
Plt	56.6×10^6/mL	Pi	8.0 mg/dL	Na	67 mEq/L
		Mg	3.8 mg/dL	K	31 mEq/L
Blood chemistry		CRP	0.78 mg/dL	Cl	42 mEq/L
AST	31 IU/L	Ionized ca	1.18 mmol/L	Cre	47.9 mg/dL
ALT	20 IU/L	25VD	15.1 (9–33.9) ng/ml	Osmolarity	323 mOsm/L
ALP	437 IU/L	1.25VD	14 (20–60) pg/ml	TTKG	8.3
BAP	30.4 mg/L	ACE	33.1 (7.7–29.4) IU/I	BMG	51.78 mg/dL
g-GTP	34 IU/L	Osmolarity	288 mOsm/L		
LDH	310 IU/L				
Total protein	7.8 g/dl			pH	7.495
Albumin	3.6 g/dL	*Endocrinological findings*		PCO_2	36.9 mmHg
Urea nitrogen	79.9 mg/dL	iPTH	52 (10–65) pg/ml	PO_2	93.4 mmHg
Creatinine	5.63 mg/dL	PTHrP	<1.1 pmol/L	HCO_3	28.1 mmol/L
Urea acid	6.3 mg/dL	PRA	91.8 ng/mL/h	Base excess	5.0 mmol/L
		Aldosterone	1040 pg/mL		

VD vitamin D, *ACE* angiotensin-converting enzyme, *iPTH* intact parathyroid hormone, *PTHrP* PTH-related protein

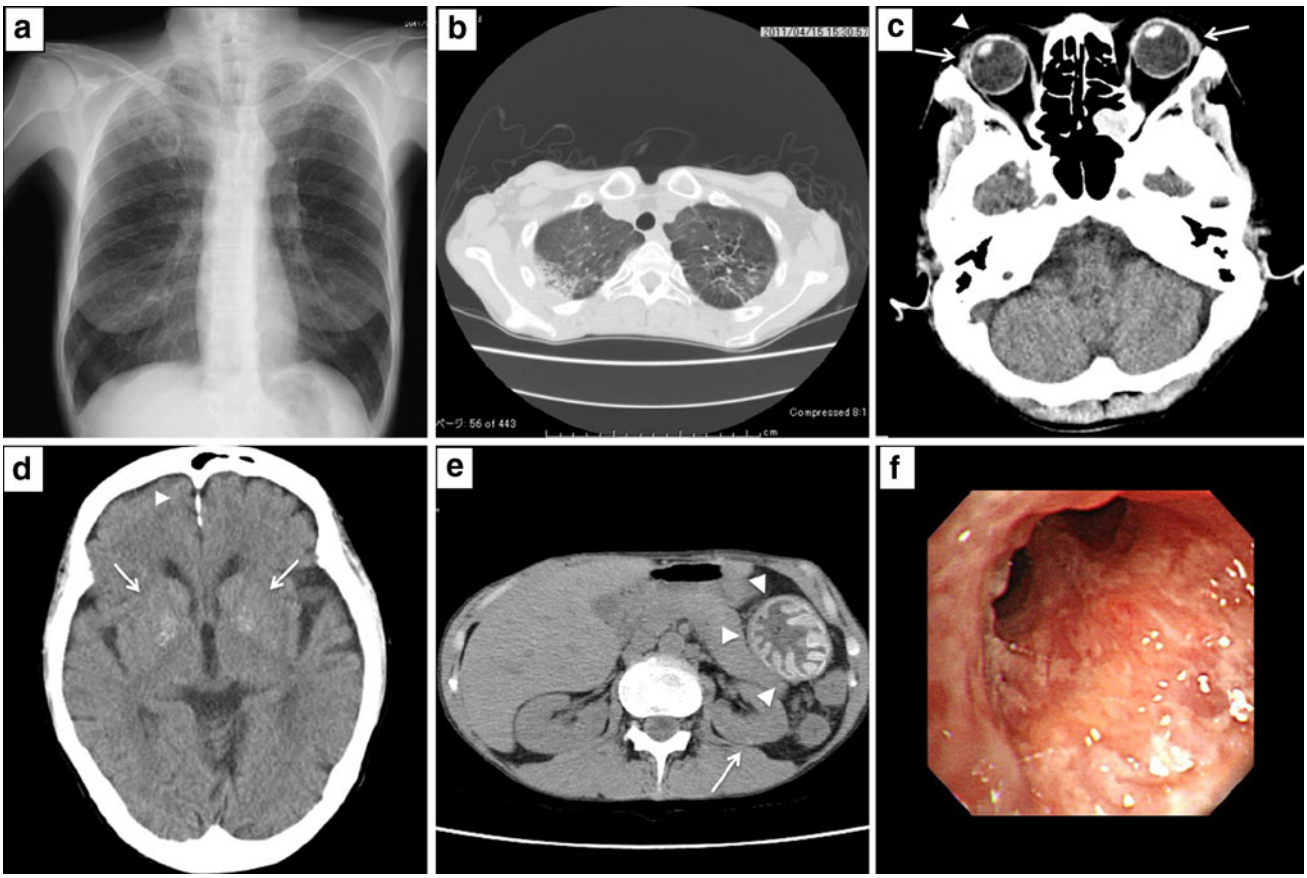

Fig. 1 **a** Chest roentgenogram revealing a tumor lesion in the right upper lung and slight diffuse shadows in the bilateral upper lungs. **b** Computed tomography revealed diffuse ground-glass opacities in the bilateral upper lungs and a tumor-like lesion with a cavity in the right upper lung. **c**, **d**, **e** Computed tomography revealed multiple organ calcification: in the cornea (**c**; *arrowhead*) bulbar conjunctiva (**c**; *arrows*), falx cerebri (**d**; *arrowhead*), globus pallidus (**d**; *arrows*), gastric mucosa (**e**; *arrowheads*), and kidney (**e**; *arrow*). **f** Bronchoscopy revealed a diffuse white nodular lesion on the surface of the trachea

her height was 155 cm, body weight was 35.5 kg, and body mass index was 15.5 kg/m^2. While she had been diagnosed with depression, her food intake habit was normal and she was not anorexic. On admission, her body temperature was 36.8 °C, blood pressure was 116/74 mmHg, heart rate was 94 beats/min, respiratory rate was 15 breaths/min, and oxygen saturation was 100 % while breathing ambient air. She did not show dryness of oral mucosa and edema of lower legs. Results of physical examination were otherwise unremarkable, including neurological examinations. Laboratory findings during admission revealed hypercalcemia, hyperphosphatemia, and an elevation in serum creatinine levels. Despite the renal dysfunction, blood pH revealed alkalemia. Other laboratory findings are presented in Table 1. No parathyroid adenoma was shown on computed tomography, and no ^{99m}Tc-hexakis-2-methoxyisobutylisonitrile (MIBI) scintigraphy uptake was detected. Other granulomatous diseases presenting hypercalcemia, such as sarcoidosis or tuberculosis have been denied. Chest roentgenography revealed a tumor-like lesion in the right upper lung, and slight diffuse shadows in the bilateral upper lungs (Fig. 1a). Chest computed tomography (CT) revealed diffuse ground-glass opacities in the bilateral upper lungs, and a tumor-like lesion with a cavity in the right upper lung (Fig. 1b) and gastric wall calcification (Fig. 1e). Uptake on ^{99m}Tc-methylene diphosphonate scintigraphy (^{99m}Tc-MDP) was increased in the bilateral upper lungs and gastric wall (Fig. 3a), and the uptake on ^{67}Ga-citrate scintigraphy also increased in the bilateral upper lungs (Fig. 3b). Bronchoscopy revealed a diffuse white nodular lesion on the surface of the trachea (Fig. 1f), and histopathological examination of the bronchial mucosa and gastric wall revealed calcified lesions (Fig. 2). The patient was diagnosed with metastatic calcification of the lungs and stomach. Other calcifications were found in the cornea (Fig. 1c), bulbar conjunctiva (Fig. 1c), falx cerebri (Fig. 1d), choroid plexus, and globus pallidus (Fig. 1d) on brain CT (Fig. 1c, d). Although small renal calcifications were found (Fig. 1e), no urinary stone was seen on CT.

After admission, the patient was administered saline and oral medications were discontinued, with the exception of

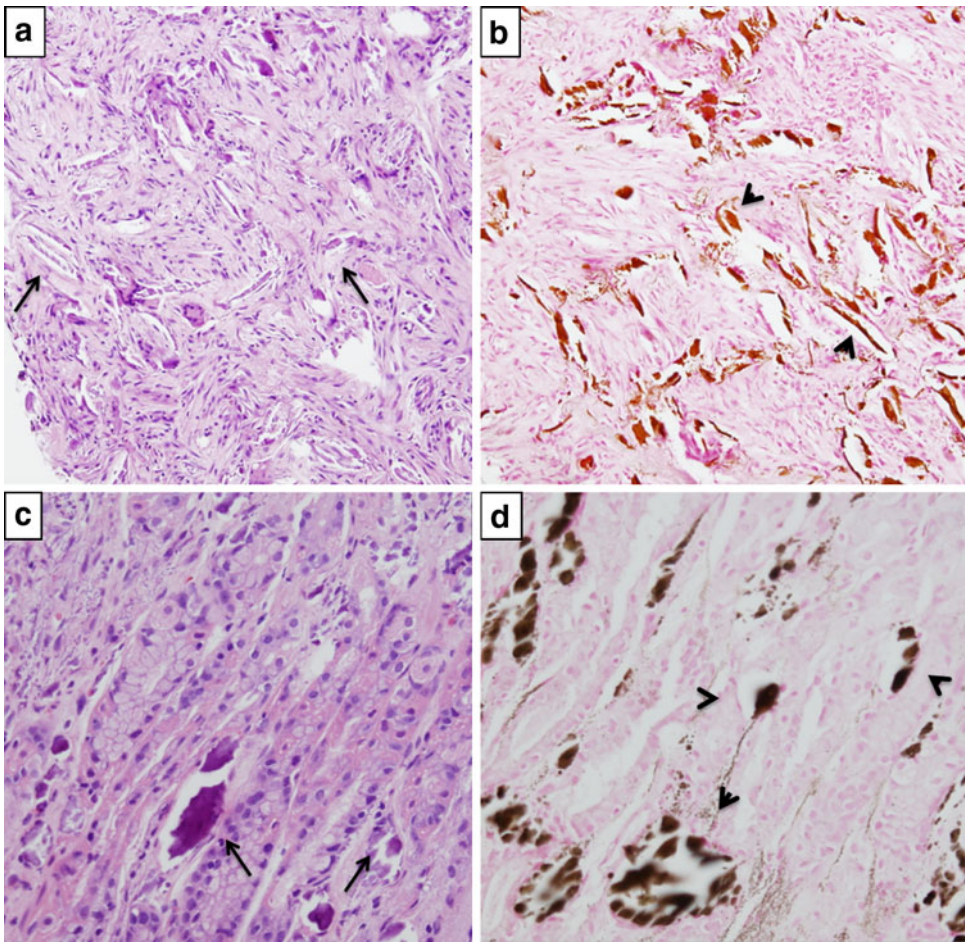

Fig. 2 Histopathology of the bronchial mucosa revealed calcified lesions via H&E stain (**a**; *arrows*) and von Kossa stain (**b**; *arrowheads*), and gastric mucosa revealed calcified lesions via H&E stain (**c**; *arrows*) and von Kossa stain (**d**; *arrowheads*)

antidepressants. Serum creatinine levels gradually decreased to 3.2 mg/dl and serum calcium phosphate levels decreased to 57 mg^2/dl^2 on day 12 after admission, while the serum calcium level was not ameliorated. On day 13 after admission, foot edema was detected. She therefore restarted taking diuretics, comprising furosemide (40 mg/day), spironolactone (50 mg/day), and potassium chloride (1800 mg/day). Arterial pH and HCO_3^- levels gradually decreased from 7.495 to 7.388, and 28.1 to 18.5, respectively, on day 25 after admission. The parathyroid hormone (PTH) level decreased to 15 pg/ml, accompanying a drop in calcium phosphate levels (Fig. 4).

Three months later, CT revealed continued ground-glass opacities in the bilateral upper lungs and a tumor-like lesion in the right upper lobe, but no worsening was apparent, and her cough had disappeared.

Discussion

Metastatic calcification is mainly caused by secondary hyperparathyroidism in the presence of CRF. However, the development of severe metastatic calcification that is radiographically visible, as was evident in the present case, is uncommon. Metastatic calcification primarily occurs in organs accustomed to an alkaline environment, such as the stomach, kidneys, and lungs, which secrete free hydrogen ions. Patients with CRF usually present with metabolic acidosis that may protect them from tissue calcification. Despite the presence of CRF in the present case, the patient displayed alkalosis, and was therefore susceptible to accelerated tissue calcification.

Milk-alkali syndrome consists of renal failure, hypercalcemia, and metabolic alkalosis, and is accompanied by early renal dysfunction. Among patients with impairment of renal function, milk-alkali syndrome is a major cause of hypercalcemia [4]. Patients with normal renal function can usually excrete excess calcium and bicarbonate, and are therefore not threatened by the risk of hypercalcemia and metabolic alkalosis. Milk-alkali syndrome will therefore arise in patients with decreased renal function. In the present case, the daily intake of calcium was 420 mg. This amount is not usually sufficient to cause milk-alkali syndrome. In the present case, pre-existing renal failure attributed to long-term use of furosemide was considered

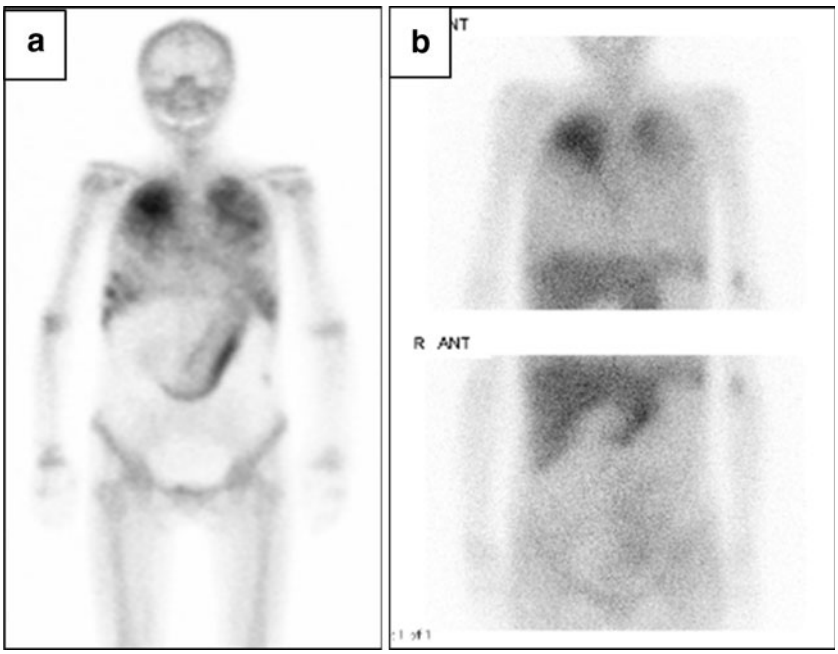

Fig. 3 **a** Uptake of ^{99m}Tc-MDP was increased in the bilateral upper lungs and gastric wall. **b** Uptake on ^{67}Ga-citrate scintigraphy was increased in the bilateral upper lungs

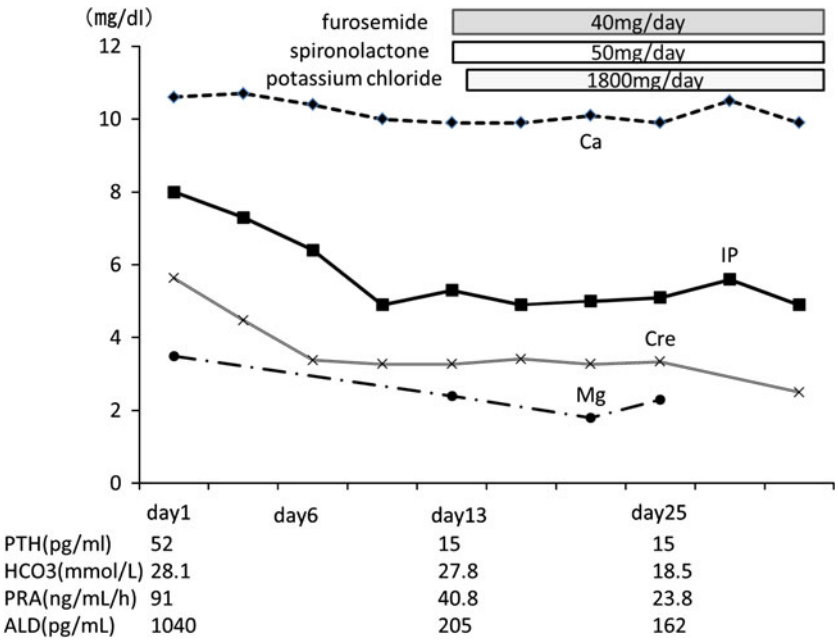

Fig. 4 Clinical course from admission

responsible for the development of milk-alkali syndrome [5, 6]. Furosemide inhibits the Na–K–2Cl cotransport system in the loop of Henle, reduces fluid reabsorption, and leads to hypokalemia and metabolic alkalosis. In addition, long-term exposure to furosemide may cause interstitial inflammatory cell infiltration, fibrosis, calcification and tubular atrophy, and deteriorate the glomerular filtration rate. This is referred to as pseudo-Bartter syndrome [7]. In this case, the patient had been in metabolic alkalosis and renal insufficiency caused by furosemide abuse. Thus, even small doses of vitamin D, calcium phosphate, and bicarbonate may have contributed, at least in part, to the development of milk-alkali syndrome. Although furosemide increases Ca^{2+} excretion under appropriate volume expansion, extracellular fluid (ECV) depletion limits Ca^{2+} excretion by reducing the glomerular filtration rate (GFR) and enhancing proximal Ca^{2+} reabsorption, which in turn induces metabolic alkalosis. Metabolic alkalosis promotes Ca^{2+} absorption in the proximal tubule and deteriorates hypercalcemia. Thus, in the present case, furosemide did not increase calcium excretion because the patient was in a dehydrated state.

Although serum PTH levels should have been suppressed under hypercalcemic conditions via negative feedback, PTH levels in the present case were elevated despite high serum calcium levels. Our speculations regarding the potential mechanisms are as follows: (1) the sensitivity of calcium-sensing receptors (CaSR) was suppressed due to CRF, so serum PTH levels were relatively high despite the hypercalcemia; (2) serum ionized calcium levels were not high because of alkalosis; and (3) the degree of serum calcium change promoted PTH secretion. Serum calcium levels would then fall after admission, and PTH secretion would be suppressed in turn [7]. In one case reported elsewhere, amino-terminal PTH was elevated to 1000 pg/ml (normal: <120 pg/ml) in a patient with milk-alkali syndrome, and this elevation in amino-terminal PTH was caused by renal failure [8]. In contrast, serum intact PTH (i-PTH) levels are unaffected by renal function; as such, serum iPTH levels have recently been reported to be normal in milk-alkali syndrome. Primary hyperparathyroidism was not likely, as parathyroid swelling was not detected on ultrasonography and abnormal uptake was not detected with MIBI scintigraphy.

Several cases of metastatic calcification, as identified by ^{99m}Tc-MDP, have been reported prior to the development of CRF in patients [9, 10]. Pulmonary uptake on ^{67}Ga-citrate scintigraphy was also used to detect metastatic calcification in the present case, similar to a report by Sullivan [11]. Chest roentgenography and CT only detected ground-glass shadows and a tumor-like lesion in the upper lung lobe. These changes are not specific to metastatic calcification, so ^{99m}Tc-MDP and ^{67}Ga-citrate scintigraphy are usually used to detect metastatic calcification.

It is recommended that serum calcium and phosphate concentrations should be reduced to manage metastatic calcification. In the present case, although calcium and phosphate concentrations gradually reduced after initiating saline infusion and discontinuing alfacalcidol, furosemide, and stomach pain medicines for several days, calcium and phosphate concentrations did not reach normal levels (i.e., under 40 mg^2/dl).

We have reported on a case with severe metastatic calcification due to milk-alkali syndrome, which was exacerbated by multiple factors, including oral alkaline medications, such as sodium bicarbonate and calcium carbonate, and pseudo-Bartter syndrome resulting from long-term furosemide abuse.

Conflict of interest The authors declare that they have no competing interests.

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