Acute cardiac damage and acute kidney injury associated with hypercalcemia crisis in hyperparathyroidism: a case report

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Abstract
Hyperparathyroidism-induced hypercalcemic crisis is a rare presentation of primary hyperparathyroidism. Primary hyperparathyroidism is caused by uncontrolled and immoderate secretion of parathyroid hormone. The most common presentation in primary hyperparathyroidism is renal stones, soft tissue calcification, cystic bone disease, and even hypercalcemic crisis. We report a patient who presented with multiple organ dysfunction syndrome due to extreme hypercalcemia (serum calcium concentration, 4.79 mmol/L [2.15–2.25 mmol/L]) resulting from primary hyperparathyroidism (serum parathyroid hormone concentration, 2215 pg/mL). The complications in this patient were complete cardiac damage and acute kidney injury. On the basis of the hypercalcemic crisis, the patient subsequently underwent surgical resection of parathyroid adenoma. Two days after surgery, her serum calcium and parathyroid hormone concentrations were normal. The patient had a good recovery after a series of other relevant therapies. In conclusion, surgery should be taken into consideration for hyperparathyroidism.

Keywords
Acute cardiac damage, kidney injury, hypercalcemic crisis, hyperparathyroidism, parathyroid adenoma, shock

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder. The incidence of PHPT is estimated to be 20/100,000 and more than 80% of cases are asymptomatic in the early stage.1 Approximately 85% of
PHPT is caused by a single parathyroid adenoma, multiple adenomas, or four-gland hyperplasia (15%), and is rarely caused by parathyroid carcinoma (<1%). The pathogenesis of PHPT is unclear in most patients. The \textit{CCND1} and \textit{MEN1} genes contribute to the development of PHPT. Somatic mutations in \textit{MEN1} occur in 12% to 35% of sporadic adenomas, whereas rearrangement or overexpression of \textit{CCND1} can occur in 20% to 40%. In PHPT, there is loss of normal feedback suppression of serum calcium concentrations on the synthesis and secretion of parathyroid hormone (PTH). This occurs because of an increased parathyroid cell mass and a reduction in the number of calcium-sensing receptor proteins in parathyroid cells. As a result, increased calcium concentrations are required to suppress PTH concentrations.

When assessing PHPT, PTH concentrations should be measured with an intact second-generation PTH assay or a third-generation assay. The treatment for PHPT includes surgery and non-surgical monitoring and management. Parathyroidectomy remains the only cure for PHPT and is recommended in all symptomatic patients. Unfortunately, no currently available single drug can treat PHPT.

Hyperparathyroidism-induced hypercalcemic crisis (HIHC) is a rare, but life-threatening, symptom of PHPT. The course of this disease can be complicated by multiple concurrent comorbidities, including acute kidney injury, cardiac arrhythmias, severe hypovolemic shock, and various gastrointestinal disorders. Despite these challenges, patients with HIHC can be successfully treated with intensive medical support and emergent parathyroidectomy, and they have a good recovery. Severe PHPT is a rare condition. We report a patient who presented with multiple organ dysfunction syndrome due to extreme hypercalcemia resulting from PHPT. We present the following article in accordance with the CARE guideline checklist.

**Case presentation**

A 43-year-old woman presented to the emergency room following 2 weeks of severe subxiphoid pain and sudden oliguria for 2 days. The initial symptoms of the patient consisted of sudden onset of epigastric pain, especially in the subxiphoid area, followed by weakness, bloating, nausea, and vomiting. These symptoms became aggravated without medical treatment and the patient was admitted to the medical intensive care unit in a conscious state. She had no prior medical history of diabetes, hypertension, cerebrovascular disease, hypercalcemia, or cardiovascular disease. Her temperature, heart rate, respiratory rate, and blood pressure were normal. There was neither abnormal lung sounds nor cardiac murmur on a physical examination.

Before being admitted to our hospital, her initial laboratory examination results were remarkable, including an elevation in serum concentrations of calcium (5.5 mmol/L, normal value: 2.15–2.25 mmol/L), uric acid (773.7 μmol/L, 90–450 μmol/L), creatinine (323 μmol, 46–92 μmol), and troponin I (26.4, ng/mL, 0–0.034 ng/L). The patient was instantly transferred to our medical intensive care unit because of the hypercalcemic crisis, accompanied by myocardial damage and acute kidney injury. The patient completed a series of laboratory evaluations. A blood test showed a white blood cell count of \(34.82 \times 10^9/L\) (3.5–9.5 \times 10^9/L) (89.5% neutrophils) and a platelet count of \(449 \times 10^9/L\) (125–350 \times 10^9/L). The acute kidney injury was indicated by a urea concentration of 649 μmol/L (90–450 μmol/L) and a creatinine concentration of 203.7 μmol (46–92 μmol). The representative diagnostic markers of myocardial damage were as
follows: troponin I concentration, 24.79 ng/mL; creatine kinase isoenzyme concentra-
tion, 66.10 ng/mL (0–2.02 ng/mL); myohe-
moglobin concentration, 8025 ng/mL (0–61.5 ng/mL); glutamic-oxalacetic trans-
aminate concentration, 305 μL (14–36 μL); circulating myocardial microRNA (from
an infarcted heart), 58,000 pg/mL (0–125 pg/mL), serum calcium concentration,
4.79 mmol/L (2.15–2.25 mmol/L), and serum PTH concentration, 2215 pg/mL
(15–65 pg/mL).

Computed tomography showed small stones in both kidneys, sporadic inflamma-
tion of the lungs, and a 22 × 27-mm mass in the right neck near the right thyroid gland
(Figure 1). Electrocardiography showed nodal tachycardia with a ventricular
premature beat, and T wave changes with subendocardial myocardial infarction. The
patient was advised to have myocardial enzymes tested. B-mode ultrasound
showed an 18 × 15 × 11-mm mass, with an obscure boundary and morphological
irregularity.

On the basis of her clinical manifesta-
tions combined with biochemical parame-
ters, she was diagnosed with myocardial
damage, renal injury, shock, hypercalcemia,
and PHPT. Her shock was emergently
treated with aggressive intravenous fluid
resuscitation, and medical dopamine and
noradrenaline were used to elevate her
blood pressure. She was also administered
milrinone to strengthen her heart rhythm
and phosphagen to nourish the myocardi-
um. Her hypercalcemia was treated with
calcitonin, bisphosphonates, glucocorti-
coids, furosemide, and continuous renal
replacement therapy via a temporary
venous catheter. However, her serum calci-
um concentrations remained high. She sub-
sequently agreed to having parathyroid
exploration and right parathyroidectomy
after a discussion with her relatives regard-
ing her cardiovascular and renal disorders
along with multiple organ dysfunction syn-
drome. The patient was intubated in the
operating room and a 30 × 20-mm hyper-
plastic parathyroid mass on the inferior
aspect of the right thyroid lobe was excised
during the surgery (Figure 2a). The gland
was brittle and contained an irregular
boundary. The tumor was dissected free
from surrounding edematous tissues with
difficulty. The diagnosis of right parathy-
roid adenoma was confirmed by a histo-
pathological examination (Figure 2b, c, d).

Figure 1. Neck computed tomography scan. (a) Neck computed tomography shows a mass in the arterial
phase. (b) Neck computed tomography shows a mass in the venous phase. The red arrows indicate a
parathyroid tumor.
After the operation, the patient was immediately admitted to the intensive care unit and treated with mechanical assistance, sedation and analgesia, myocardial nutrients, anti-inflammatory medication, and nutritional support.

PTH and serum calcium concentrations were measured on the second day after surgery. The PTH baseline concentration of 2215 pg/ml was decreased to 66 pg/mL and the serum calcium concentration was decreased from 4.79 mmol/L to 2.66 mmol/L following resection of the parathyroid adenoma. A pathological examination of the gland identified some features of malignancy, with proliferating small round cells, including partly capsular invasion to adipose tissue, nested cells, and abundant sinusoids. The tumor was classified as an atypical parathyroid adenoma.

In the postoperative period, serum PTH and calcium concentrations rapidly decreased (Figure 3), and the patient gradually recovered over the next week. The patient was discharged 3 weeks after surgery.

Discussion

PHPT and malignancy are the primary cause of hypercalcemia.10,11 The most common cause of PHPT is parathyroid gland adenomas (80%–85%), while carcinoma, parathyroid hyperplasia,
parathyroid cyst, and multiple endocrine neoplasia types 1 and 2A are rare pathogen-
eses.12 The symptoms of PHPT are initially mild or asymptomatic, followed by bone, neuromuscular, digestive, and kidney symp-
toms. Despite the various clinical manifesta-
tions of PHPT, hypercalcemia is the most
common symptom in clinical cases.

Some studies provided an unclear defini-
tion of hypercalcemic crisis as a serum
calcium concentration >3.5 mmol/L, accom-
panied by signs and symptoms.13,14 A hypercalcemic crisis was first described
in 1939 by Hanes, and is considered as an
endocrine emergency and fatal in the
absence of optimal treatment.15 Patients
with hypercalcemia due to PHPT show
changes in cardiac physiology and struc-
ture, including diastolic dysfunction, cardia-
cal and vascular calcification, and left
ventricular hypertrophy.16

In a study of 67 patients with HIHC,
only two patients suffered from cardiac
arrhythmias.8 However, severe cardiac
arrhythmias are complications of hypercal-
cemic crisis. Three mechanisms are involved
in the development of hypercalcemia-
induced acute heart failure. One mechanism
is intracellular hypercalcemia, which can
impair myocardial repolarization coupling
and reduce diastolic relaxation capacity,
contributing to the development of heart
failure.17 Another mechanism is that accu-
mulation of calcium can promote myocar-
dial contraction band necrosis, which is
characterized by excessive contraction of
myofibrils and subsequent myocytolysis.18
Additionally, catecholamines can markedly
increase intracellular calcium concentra-
tions,18 consequently contributing to hemo-
dynamic instability.

The acute effects of PHPT on renal func-
tion are not well understood. Moreover,
on-oliguric acute kidney injury caused by
refractory hypercalcemia requires emergent
hemodialysis. Measuring concentrations of
serum calcium and PTH is important for an
early diagnosis, estimating disease severity,
and treatment. When patients with acute
cardiac damage and acute kidney injury
have no obvious causes and elevated
serum calcium concentrations are observed,
PHPT-induced cardiac damage should be
suspected. The treatment of hypercalcemia
includes forced diuresis, bisphosphonates,
oral phosphates, hydration with saline, cal-
citonin, glucocorticoids, and dialysis.
Patients with sudden oliguria should be
immediately treated with CRRT.

Imaging techniques help surgeons to
locate adenomas and target the appropriate
surgical area in PHPT.9 Unfortunately, our
patient who was treated with invasive respira-
tory support therapy was instantly trans-
ferred to the medical intensive care unit
without Tc 99m-sestamibi scintigraphy.
She had surgery performed after supportive
treatment. After surgery, her serum calcium
concentrations were greatly decreased,
respiratory support was stopped, myocar-
dial injury indicators gradually decreased,
and her renal function gradually recovered.
The patient was satisfied because the sur-
gery and treatment saved her life. Our find-
ings suggest that when patients with similar
symptoms to those found in our patient are
encountered in the clinical setting, the pos-
sibility of PHPT should be considered.

**Ethics statement**
The reporting of this study conforms to the
CARE guidelines.19 Detailed patient informa-
tion has been de-identified. The study protocol
was approved by the ethics review committee of
Northern Jiangsu People’s Hospital. The patient
provided consent for the treatment. Written
informed consent was obtained from the patient
for publication of this case report and the
accompanying images.

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