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A Morishita and others

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Effect of early dose increase of evocalcet for intractable hypercalcemia caused by parathyroid carcinoma

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Summary

Hypercalcemia due to parathyroid carcinoma (PC) is safely and quickly controlled with rapidly increasing evocalcet doses. Most parathyroid carcinomas are detected because of hypercalcemia due to primary hyperparathyroidism (PHPT). Hypercalcemia becomes more severe in patients with PC than those with parathyroid adenoma or hyperplasia. Hypercalcemia often causes renal dysfunction, gastrointestinal symptoms, and psychiatric symptoms. Consequently, the serum calcium level needs to be promptly corrected. Here, we report a case of PC with remarkably persistent hypercalcemia, which we safely and quickly controlled with rapidly increasing evocalcet doses. A 77-year-old female presented with renal dysfunction. Her serum calcium (Ca) and intact parathyroid hormone serum levels were 13.9 mg/dL and 1.074 pg/mL, respectively. Her renal function worsened because of hypercalcemia due to PHPT. Technetium-99 m methoxy-isobutyl-isonitrile parathyroid scintigraphic examination revealed an accumulation below the right thyroid lobe. CT examination showed a 35-mm mass. Hypercalcemia needed to be immediately corrected because of the patient's worsening renal function. Evocalcet treatment at a gradually increasing dose of up to 20 mg over 3 weeks allowed her serum Ca level to be maintained below 11 mg/dL. Only mild nausea was observed at the beginning of the treatment. The mass was suspected as PC because the hypercalcemia was refractory to high-dose evocalcet. The patient was treated with parathyroidectomy and ipsilateral thyroidectomy. PC was diagnosed based on the pathological findings of capsular and venous invasion. The patient's renal function improved and surgery could be safely performed by promptly correcting hypercalcemia.

Learning points

- Hypercalcemia due to parathyroid carcinoma (PC) is often more severe than that caused by parathyroid adenoma or hyperplasia.
- PC is a rare disease, but it should be considered if the patient has intractable hypercalcemia due to primary hyperparathyroidism (PHPT).
- Evocalcet, which is used to treat hypercalcemia due to PHPT, does not interact with P450 (CYP) and causes few side effects.
- Complications, including renal dysfunction, were improved and the surgery could be safely performed by promptly correcting hypercalcemia.
- PC has a high recurrence rate. *En-block* excision is necessary when PC is suspected.

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Background

Parathyroid carcinomas (PCs) are often found together with hypercalcemia due to primary hyperparathyroidism (PHPT). Hypercalcemia is often more severe than that caused by parathyroid adenoma or hyperplasia, thereby causing renal dysfunction, gastrointestinal problems, and psychiatric symptoms (1, 2, 3). Thus, promptly correcting the serum calcium level is necessary for patients with PC.

In recent years, calcimimetics have been used to treat PHPT-induced hypercalcemia. However, cinacalcet, which was the first oral calcimimetic to be released, has reported gastrointestinal symptoms as a class effect frequently, sometimes leading to treatment interruption (2). Conversely, evocalcet, which was the second released oral calcimimetic, causes few side effects, especially gastrointestinal symptoms (2).

A phase III study of evocalcet in Japan revealed that 77.8% of patients with hypercalcemia due to intractable PHPT, postsurgical recurrence and PC achieved normal serum Ca level. However, controlling the serum Ca concentration took 12 weeks, and none of the patients with PC achieved the numerical target (4). Estimating the effects of calcimimetics on hypercalcemia takes time because calcimimetics are recommended to be increased every 2 weeks. However, promptly evaluating the effect of calcimimetics and correcting the serum calcium level is necessary for patients with PC because of organ derangement.

Here, we report a case of PC-induced intractable hypercalcemia which caused renal dysfunction. We were able to promptly correct serum calcium, improve renal function, and safely perform radical surgery by gradually increasing the evocalcet dosage for >3 weeks without side effects.

Case presentation

A 77-year-old female presented with renal dysfunction and a palpable hard mass on the right side of the neck. The mass had first been recognized 2 years before the presentation and remained in size. The patient had a medical history of hypertension but no fractures or renal calcification. There were family histories of colon, lung, and pharyngeal cancers but not hyperparathyroidism. On the day of admission, the patient was conscious with a body weight of 44.2 kg and BMI of 17.7 kg/m^2. There was no lymphadenopathy.

Investigation

Blood examinations revealed renal function impairment (serum creatinine (Cre): 1.46 mg/day), hypercalcemia (serum calcium (Ca): 13.9 mg/dL), and hypophosphatemia (serum phosphorus (P): 2.4 mg/dL) (Table 1). The serum intact parathyroid hormone (i-PTH) level was greatly elevated at 1.074 pg/mL (Table 1). Technetium-99 m methoxy-isobutyl-isonitrile (Tc-99 m MIBI) parathyroid scintigraphic examination showed an accumulation in the lower right parathyroid gland that was washed out in delayed images (Fig. 1). Ultrasonography of the neck showed a hypoechoic heterogeneous mass of approximately 25.5 × 20.3 × 34.5 mm^3 below the right thyroid lobe (Fig. 2). CT imaging revealed a 35-mm mass below the right thyroid lobe. The mass had a slightly irregular margin, and infiltration into the thyroid gland was not confirmed (Fig. 3). Additionally, the patient

Table 1 Laboratory data on admission and before the operation.

	On admission	Pre-operation	Post-operation	Normal range
Albumin, g/dL	4.5	4.3	4.2	4.1–5.1
Calcium, mg/dL	13.9	10.8	9.9	8.8–0.1
Phosphorus, mg/dL	2.4	2.8	4.7	2.7–4.6
BUN, mg/dL	34.2	35.3	36	8.0–20.0
Creatinine, mg/dL	1.46	1.27	1.44	0.46–0.79
ALP (JSCC), U/L	382	382	349	106–322
i-PTH, pg/mL	1074	671	14	10–65
1, 25-(OH)2-D3, pg/mL	98	No data	24	20–60
TRACP-5b, mU/dL	967	No data	172	120–420
Total P1NP, ng/mL	97.6	No data	128.8	26.4–98.2
Urinary calcium, g/g × creatinine	0.23	0.27	0.08	0.05–0.15
FECa, %	1.31	3.15	1.18	2–4
%TRP	58	61	83	60–90

1, 25-(OH)2-D3, 1, 25 dihydroxy vitamin D3; ALP, alkaline phosphatase; BUN, urea nitrogen; FECa, fractional excretion of calcium; i-PTH, intact parathyroid hormone; P1NP, type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b; TRP, tubular reabsorption of phosphate.

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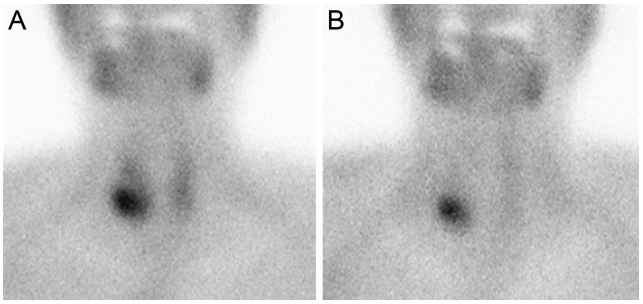

Figure 1
Technetium-99 m methoxy-isobutyl-isonitrile (Tc-99 m MIBI) parathyroid scintigraphic examination. An early anterior–posterior scan of the neck shows an accumulation in the lower right parathyroid gland (A). A delayed anterior–posterior scan of the neck shows incomplete washout of radiotracer in the lower right parathyroid gland (B).

had osteoporosis, with a decreased bone density T-score in her lumbar vertebra of −3.2. The tartrate-resistant acid phosphatase 5b (TRACP 5b) level, which is a bone resorption marker, was elevated at 967 ng/mL (Table 1). Consequently, she was diagnosed with PHPT originating in the lower right parathyroid gland.

Treatment

The patient's renal function had been decreasing; thus, her hypercalcemia needs to be immediately corrected. Evocalcet was started in combination with i.v. isotonic normal saline and elcatonin. The dose of evocalcet was increased early assuming treatment resistance because CT imaging had not ruled out PC. The patient complained of mild nausea after evocalcet administration, but this was improved by antiemetics. Afterward, there were no side effects. However, the hypercalcemia could not be controlled below 11.5 mg/dL even with evocalcet

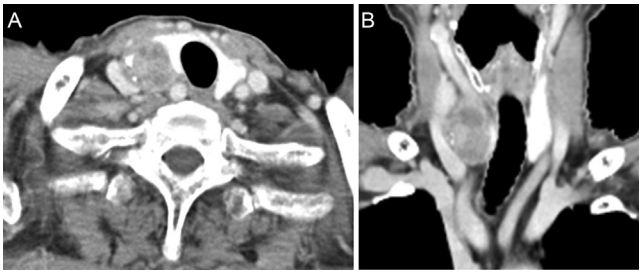

Figure 3
CT scan of the neck. A CT image revealed a 35-mm mass below the right thyroid lobe. The mass had a slightly irregular margin.

administration of 16 mg for 2 weeks plus i.v. zoledronate of 3 mg. We chose a reduced zoledronate dosage because of the patient's renal insufficiency. Therefore, evocalcet dosage was increased to 20 mg, whereupon the Ca level was maintained at 10.5 mg/dL (Fig. 4). This procedure with evocalcet was approved by the ethical committee of Yaizu City Hospital (approved number: 2022-283). No QT prolongation was detected by electrocardiography during treatment. The Cre level improved to 1.26 mg/dL.

The tumor was assumed to be PC based on the irregular margin visible by CT imaging and the treatment-resistant hypercalcemia with high-dose evocalcet. Consequently, parathyroidectomy and right thyroid lobectomy were performed on day 55 after the treatment initiation. The tumor was easy to remove without any adhesion. The resected mass was a white solid, 3.0 cm across in its largest dimension, and was encapsulated and partially invaginated into the thyroid gland (Fig. 5). Pathological investigation revealed capsular and vascular invasion into the muscular veins outside the capsule (Fig. 6). Immunohistochemical staining was positive for GATA3 and chromogranin A, and the Ki-67 proliferation index

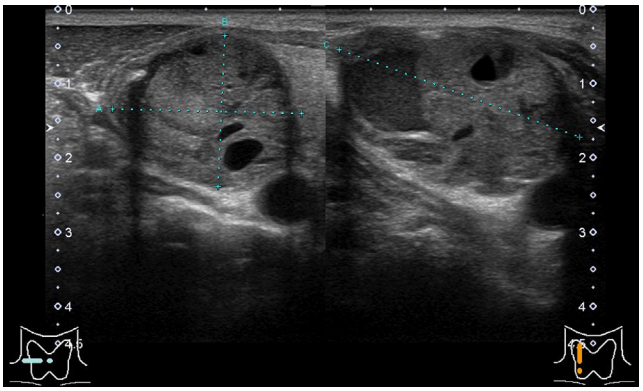

Figure 2
Ultrasonograms (US) of the neck. US image showed a 34.5 × 25.5 × 20.3-mm^3 mass below the right thyroid lobe.

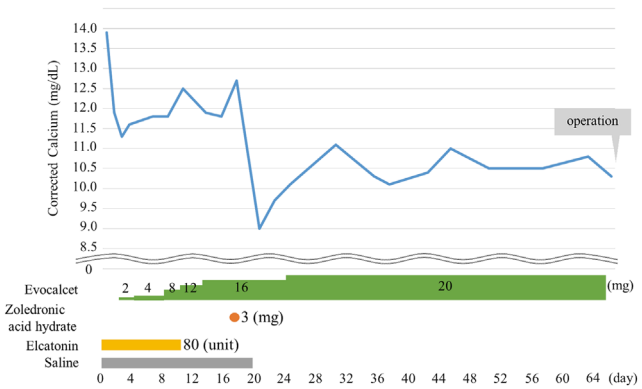

Figure 4
Graph showing the changes in serum calcium as the treatment progressed.

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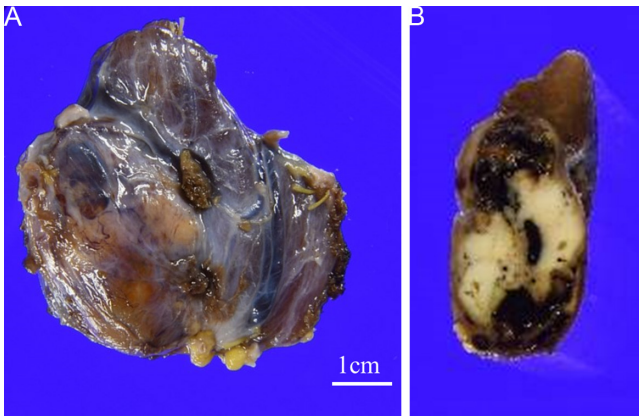

Figure 5
The resected lower right parathyroid mass and ipsilateral thyroid.

was 4.8% (Fig. 6). Based on these findings, the lesion was diagnosed as PC.

Outcome and follow-up

Postoperatively, the i-PTH level decreased to 14 pg/mL and has been maintained at a low level for 1 year. The TRACP 5b level and the bone density T-score both improved within the normal range. There has been no apparent recurrence.

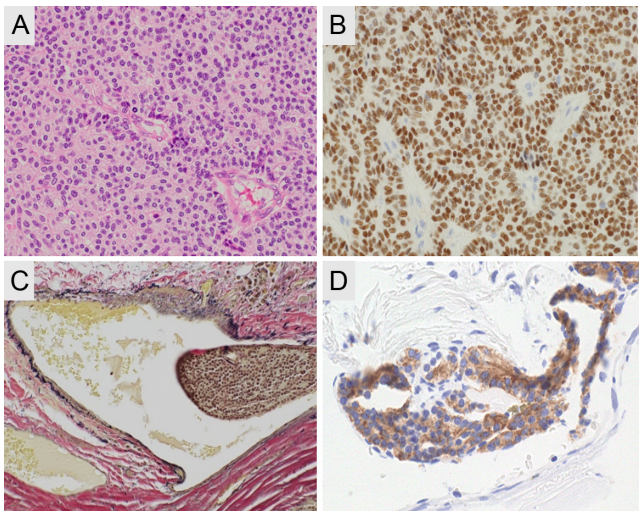

Figure 6
Histopathology and immunohistochemistry of the lower right parathyroid gland. Hematoxylin and eosin staining (HE) showed diffuse expanded tumor cells (A). Immunohistochemical staining of GATA3 showed diffuse positive staining in tumor cells (B). Vascular invasion into the muscular veins outside the capsule was observed (C). Immunohistochemical staining for PTH was positive in tumor cells invading the vasculature (D).

Discussion

A rapidly increasing evocalcet dosage was able to safely and swiftly control intractable hypercalcemia of PCs, which improved renal function and enabled a safely performed surgery. A phase I study of evocalcet revealed that the plasma drug level became steady after 24 h, while Ca and P levels, in addition to i-PTH, remained stable at 24 h after evocalcet administration (5). These results showed the same tendency at different drug doses (5). Hypocalcemia is the main side effect when increasing calcimimetics. Here, the patient's hypercalcemia could be safely improved without side effects, such as hypocalcemia and upper gastrointestinal symptoms, when the dose of evocalcet was increased earlier than 2 weeks.

In our case, evocalcet had a good effect on hypercalcemia. However, hypercalcemia with PC suggests being less effective than that with parathyroid adenoma or hyperplasia (4). A previous study revealed that 62% of patients with PC who had recurrence after parathyroid operations respond to cinacalcet calcimimetics temporarily, but the effect did not persist. Estimating the effect of calcimimetics by serum Ca level at baseline is difficult because some patients have higher Ca levels of >14.3 mg/dL who responded to the medicine (6). The serum calcium of the non-responders increased in the titration phase (6). The titration period of calcimimetics could be shortened and the effect could be evaluated quickly if we could increase the dosage of calcimimetics within <2 weeks.

A previous study revealed an improved bone mineral density with bisphosphonate administration in combination with cinacalcet for primary hyperparathyroidism but does not affect hypercalcemia (7). In this case, we determined that zoledronate was less effective because the serum Ca decreased once but increased after a few days.

In this case, PC that infiltrated into the thyroid was suspected based on treatment resistance and CT imaging. The patient underwent radical surgery, including parathyroidectomy and ipsilateral thyroidectomy, and PC was diagnosed based on the pathological findings. Reoperation is required to remove the tissues when pathological examination reveals that PC has invaded the surrounding tissue after parathyroidectomy alone. This leads to an increased risk of complications due to reoperation (8).

The patient's renal function improved and surgery could be safely performed by promptly correcting hypercalcemia. The rate of readmission after cervical

endocrine surgery has been reported as 2.8–4.0% within 30 days (9). Renal dysfunction is one of the risk factors, and the rate of readmission after cervical surgery was 17.2% in a study of patients with chronic kidney disease (CKD), which was five times higher than that in patients without CKD (10). Renal dysfunction due to hypercalcemia was observed in 84% of patients with PC (3). In this case, renal function worsened due to hypercalcemia, but the patient's renal function improved and the surgery could be safely performed by promptly correcting the hypercalcemia with rapidly-increasing evocalcet doses. The patient was not readmitted after discharge. In perioperative management, controlling hypercalcemia as soon as possible is important to improve preoperative renal function. This requires early use of increasing evocalcet doses. However, more investigations are needed to establish the safety of evocalcet.

Declaration of interest
The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement
A Morishita drafted the manuscript. Y Hozumi and G Seki reviewed and edited the manuscript. H Ishii, Y Hokazono, C M Y Kikuchi, M Shimasaki, M Itaya, M Oura, K Kuriki, and A Hishida contributed to the care of the patient.

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