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Parathyroid carcinoma with pancreatitis causing hypercalcaemic emergency treated with extracorporeal membrane oxygenation-assisted parathyroid resection

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Summary

Emergencies due to malignancies usually have a severe clinical course and require urgent treatment. These scenarios are dubbed 'oncologic emergencies'. Parathyroid tumours often cause hypercalcaemia but not oncologic emergencies. We present a case of parathyroid carcinoma with severe hypercalcaemia and pancreatitis, resolved by surgical resection of the tumour assisted by extracorporeal membrane oxygenation (ECMO). A 66-year-old woman presented to our hospital because of haematuria. Laboratory findings were as follows: white blood cell count: 30 000, C-reactive protein: 17.7, calcium: 21.9, creatine kinase: 316, creatine kinase-myoglobin binding: 20, troponin I: 1415.8, amylase: 1046, lipase: 499, blood urea nitrogen: 57, and creatinine: 2.42. ECG was unremarkable. CT revealed a 4-cm low-density irregular tumour in the left lobe of the thyroid gland and severe pancreatitis. We diagnosed hypercalcaemia and pancreatitis due to parathyroid carcinoma. Volume expansion with isotonic saline was started immediately. Calcitonin, followed by denosumab, calcimimetic agents, and continuous hemodiafiltration were administered. The patient's general condition worsened due to uncontrolled hypercalcaemia. Urgent tumour resection was planned, assisted with ECMO for cardiopulmonary support and surgical field venous pressure reduction. Tumour histology was suggestive of parathyroid carcinoma. Hypercalcaemia and the patient's general condition improved gradually postoperatively. Hypercalcaemia is one of the oncologic emergency symptoms, commonly occurring because of lytic bone metastasis. However, reports about parathyroid carcinoma-causing life-threatening hypercalcaemia and pancreatitis are scarce; the fatality of this condition is estimated to be 30–70%. We report a case of survival of hypercalcaemia of malignancy.

Learning points

- Parathyroid carcinoma is relatively rare and sometimes causes emergent conditions such as hypercalcaemia and severe pancreatitis.
- General therapy for hypercalcaemia including aggressive saline dehydration, administration of furosemide, calcitonin, zoledronic acid, and evocalcet, and dialysis is sometimes ineffective for parathyroid carcinoma. Therefore, careful planning of therapy in case of exacerbation is important.
- During an emergency, rapid surgical treatment despite high calcium level is the best potential therapeutic strategy.

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Background

Parathyroid carcinoma is a rare cause of hyperparathyroidism-induced hypercalcaemia. Sequalae of such a condition include osteopenia, renal dysfunction, and gastrointestinal upset. Here, we report a case of a woman who presented with severe hypercalcaemia (22.6 mg/dL) and was subsequently diagnosed with parathyroid carcinoma and pancreatitis, causing renal, respiratory, and circulatory dysfunction. Resolution and survival were achieved through parathyroidectomy assisted by extracorporeal membrane oxygenation (ECMO).

Case presentation

A 66-year-old woman visited our hospital's Department of Urology for haematuria accompanied by nausea. Laboratory data revealed elevations, with the reported values being the following: calcium 22.6 mg/dL; alkaline phosphatase 152 U/L; amylase 1046 U/L; lipase, 499 U/L; creatinine (Cr) 2.42 mg/dL; troponin T 1415.8 U/L; C-reactive protein (CRP) 17.79 mg/dL; and white blood cell count 30 000/μL. ECG and ultrasound were negative for ischemic heart disease. CT scan demonstrated severe pancreatitis as well as a thyroid or parathyroid tumour. Over the course of the patient's stay, the patient's blood pressure gradually dropped. Based on diagnostic test results and symptoms, the patient was diagnosed with septic shock due to pancreatitis and was immediately admitted to the intensive care unit on noradrenaline and adrenaline. Simultaneously, to decrease calcium levels, calcitonin (80 U/day) and isotonic fluids were administered. However, calcium levels did not decrease.

Investigation

The next day, laboratory tests revealed an intact parathyroid hormone level of 2204 pg/mL, and ultrasound imaging showed a 40-mm hypoechoic heterogeneous tumour with ill-defined borders in the left upper parathyroid gland. We suspected parathyroid carcinoma associated with hypercalcaemia and severe pancreatitis (Fig. 1). Enhanced CT scan was not performed due to the patient's renal dysfunction, but plain CT scan showed pancreatitis (CT grade 2). The patient had over 3 points of negative prognostic factors (shock, Cr > 2 mg/dL, and CRP 15 mg/dL). The patient was diagnosed with severe pancreatitis.

Treatment

Hypercalcaemia persisted (15 mg/dL) despite continuous hemodiafiltration (CHDF), zoledronic acid, and evocalcet administration. Altered mentation accompanying circulatory and respiratory function decline was observed; ventilator support was immediately initiated and ECMO-assisted surgery was scheduled for the next day (Fig. 2).

During surgery, we first initiated V-A ECMO for circulation support and surgical field venous return volume reduction. We performed a parathyroidectomy, left thyroidectomy, and left recurrent laryngeal nerve resection, as the tumour adhered tightly to the recurrent laryngeal nerve despite having a membrane (Fig. 3).

Outcome and follow-up

On post-operative day 1, intact parathyroid hormone (PTH) dropped remarkably. The patient's circulatory function also improved, and thus we terminated ECMO use 3 days after the surgery. Calcium levels also decreased gradually. We continued to treat pancreatitis using i.v. fluids and antibiotics. Dialysis because of remaining renal dysfunction, as well as noradrenaline, was also administered, but their use was de-escalated and finally stopped 1 month after surgery. During this period, ventilatory support had weakened the patient's respiratory muscles and she was transferred to another hospital for rehabilitation (Fig. 4).

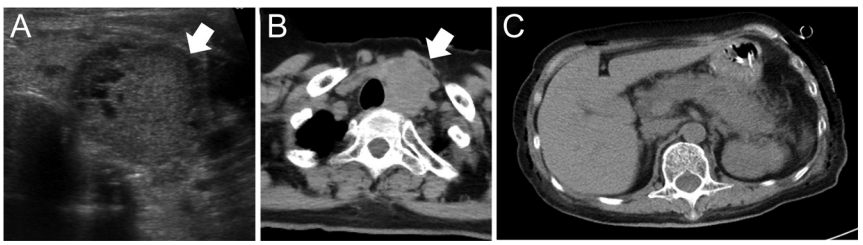

Figure 1
(A) Ultrasound examination of the left parathyroid tumour. A 37.7 × 32.3 × 30.7 mm hypoechoic heterogeneous tumour with poorly defined borders is observed. We observed a depth–width ratio > 1 and irregular borders behind the tumour, suggesting malignancy. (B) CT scan of the neck. Invasive parathyroid tumour behind the left thyroid lobe was noted. (C) CT scan of the abdomen. Enhanced CT scan was not available because of renal failure but plain CT showed pancreatic involvement; abnormal fluids were detected around the left kidney (CT grade 2 points).

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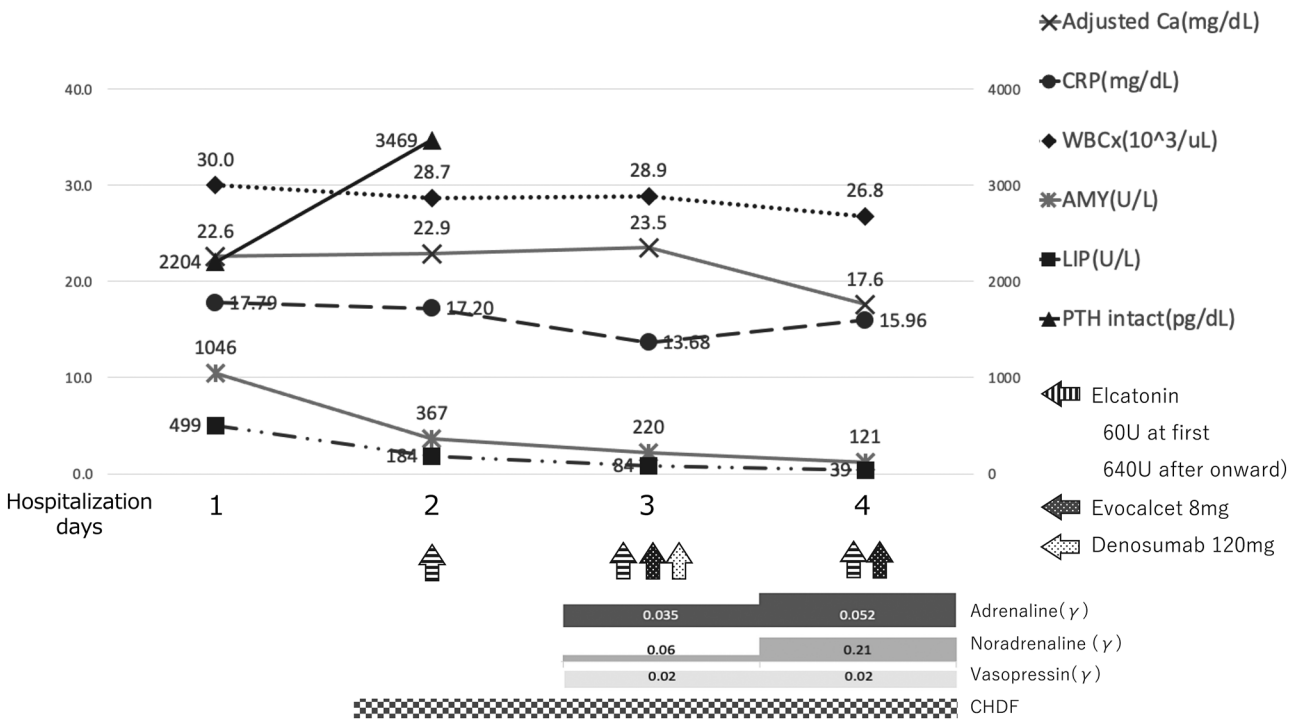

Figure 2
Process before the operation. We started administration of elcatonin (60 U/day), with isotonic fluids. On the next day, zoledronic acid and evocalcet were added and CHDF initiated. Despite those treatments, hypercalcaemia persisted, and we decided on operation assisted by ECMO.

Discussion

Hypercalcaemia occurs due to many diseases, including primary or secondary hyperparathyroidism, increased bone metabolism induced by lytic bone metastasis, or increased resorption from the kidney and intestinal tract. Hypercalcaemia is commonly caused by primary hyperparathyroidism, and adenomas account for approximately 80%, hyperplasias for 15%, and malignancies for 0.3–5.2% cases of hyperparathyroidism. The cancerous cause is relatively rare (1).

Diagnosis of parathyroid carcinoma is difficult. Preoperative pathological diagnosis with puncture aspiration cytology or biopsy is not recommended, because of the risk of tumour seeding. Therefore, clinical findings indicating malignancy are important; for example, a cervical mass is reported in 30–76% of parathyroid carcinomas (1). Hoarseness in a patient without previous cervical surgical history indicates that the patient is suffering from recurrent laryngeal nerve palsy, which is suggestive of parathyroid masses and possibly carcinoma (2).

Ultrasound findings, including a large (>3 cm) lobulated hypoechoic/heterogeneous parathyroid gland, with ill-defined borders, a thick capsule, vascularity, and calcification indicate malignancy. High depth–width ratio or high hardness on elastography are other important signs. When severe bone damage, such as that with osteitis fibrosa cystica, is observed on X-rays, or infiltration of surrounding tissues, lymph node involvement, and metastasis to other organs are observed on CT or MRI scans, parathyroid carcinoma is suspected (2).

Blood tests show that, in parathyroid carcinoma, calcium levels > 14 mg/dL or more than 3–4 mg/dL above the upper limit of normal range are observed, whereas, in parathyroid adenoma, the calcium value is seldom >1 mg/dL above the upper limit. In addition, in parathyroid carcinoma, PTH levels reach 3–10 times the value of the upper limit, while, in parathyroid adenoma, levels greater than twice the upper limit of normal are rarely seen. From those characteristics, it is generally reported that calcium levels above 12 mg/dL indicate carcinoma (2).

In our case, clinical findings, including a palpable mass, remarkably high calcium level (22.6 mg/dL), and an elevated PTH (34 times higher than the upper limit), were highly suggestive of parathyroid carcinoma. Surgery was planned without exposing the tumour.

In this case, it was difficult to determine when we had to perform surgery. To avoid ventricular arrhythmia induced by severe hypercalcaemia, we initiated preoperative medical treatment to correct serum calcium. The generally

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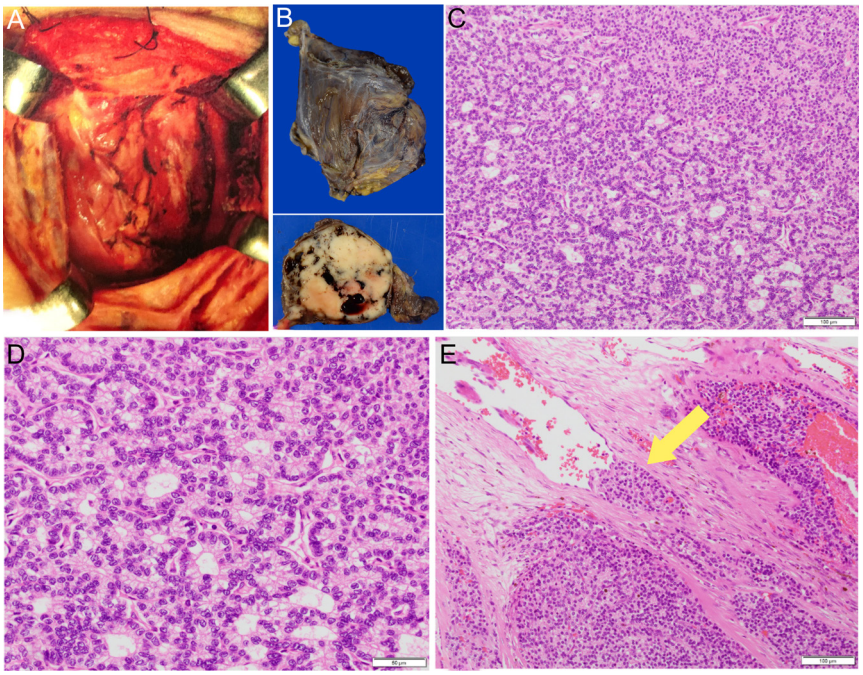

Figure 3
(A) Surgical field after the tumour is resected. (B) The parathyroid tumour. The lower photo shows the divided face of the tumour. (C) Pathology of the tumour. The fibrous band, which is thought as a sign of malignancy, was not seen in the tumour. (HE stain, ×40). (D) The palisade arrangements of tumour cells were observed. (HE stain, ×80). (E) Tumour cells were invading veins (arrow). (HE stain, ×40). (D) and E) are signs of malignancy.

recommended medical treatment for hypercalcaemia (1, 3) is summarized in Table 1 (1). We implemented aggressive dehydration with saline, involving furosemide, as well as calcitonin, dialysis, zoledronic acid, and evocalcet. Upon initiating these interventions, serum calcium dropped to a maximum of 17.6 mg/dL; subsequently, hypercalcaemic crisis was observed. We subsequently decided to perform the operation. Some reports suggest that hypercalcaemia induced by hyperparathyroidism should be managed preoperatively by medically lowering the serum calcium (4), while others recommend surgical intervention as soon as possible, regardless of calcium level (5, 6).

Iihara *et al.* mention that a hypercalcaemic crisis due to hyperparathyroidism needs to be treated with medication preoperatively. However, if the serum calcium levels of those patients are uncontrolled, prompt surgery would be recommended (7). Wang *et al.* state that reducing calcium level to 12–13 mg/dL before the operation is encouraged,

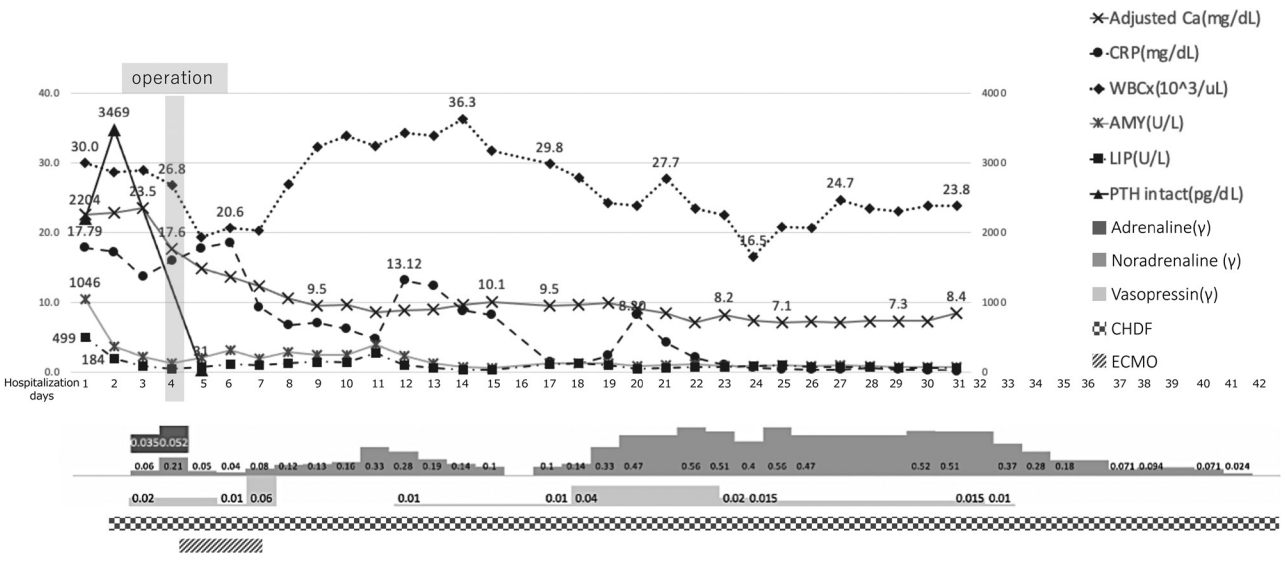

Figure 4
Progress after the operation. On post-operative day 1, the intact PTH remarkably dropped, and the circulatory condition also improved. We terminated ECMO 3 days after the surgery. The calcium level also decreased gradually. After that, treatments for pancreatitis were continued.

Table 1 Generally recommended treatment for hypercalcaemia. Interventions have various times of administration.

Treatments		Dosage and administration	Time delays
Saline		200–300 mL/h (maintaining 100–150 mL/h urine output)	Fast (12–48 h)
Calcitonin		4–8 international units/kg/6–12 h	Fast (2–4 h)
Bisphosphonates	Zoledronic acid	4 mg/day	Slow (2–5 days)
RANKL inhibitor	Denosumab	120 mg weekly for 4 weeks	Slow (2–5 days)
Calcimimetics	Cinacalcet	25 mg/12 h–75 mg/6 h	Slow (2–5 days)
	Evocalcet	2 mg/24 h–8 mg/6 h	Slow (2–5 days)
Dialysis			

but postponing the operation for 7 or 8 days in order to achieve this level is not recommended (5). Recent reports have shown that, with proper systemic management and tumour resection within 48–72 h of symptom onset, the mortality rate improves significantly from 0 to 6.8% (6, 8). Therefore, prompt surgery is required even in situations where hypercalcaemia cannot be corrected.

In our case, when deterioration of circulatory and respiratory dynamics and impaired consciousness were observed, we elected to perform the operation and save the patient's life despite uncontrolled hypercalcaemia.

In addition, primary hyperparathyroidism is sometimes associated with acute pancreatitis, but the association and mechanisms remain unclear. Khoo *et al.* report in a cohort study of patients with hyperparathyroidism that approximately 1.5% of cases were accompanied by pancreatitis, and most of them had causes of pancreatitis other than hyperparathyroidism. Therefore, no clear relationship between hypercalcaemia and pancreatitis is outlined (9). On the other hand, recent studies reported that pancreatitis in 4–7% of patients with hyperparathyroidism and especially Singh *et al*. expressed that, since 13.5% of patients with acute pancreatitis were found in the group with a high median calcium value of 15.14 ± 1.06 mg/dL, pancreatitis may be more likely to occur in severe hyperparathyroidism (10).

In conclusion, parathyroid carcinoma sometimes provokes complications such as remarkable hypercalcaemia and severe pancreatitis leading to significant emergent conditions. As parathyroid carcinoma is rare, few studies have reported therapeutic strategies for parathyroid carcinoma accompanied with an emergent condition. We believe that our study represents that careful intervention planning in case of exacerbation is important and offers a better understanding of rapid surgical intervention as a potential therapeutic approach despite high calcium levels.

Declaration of interest
The authors have nothing to disclose.

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Patient consent
The patient has provided written consent for publication of this case.

Author Contribution Statement
All authors were the members of the treating team. MT and NS were the primary surgeons who managed the patient, TM, MG, TY, NY were surgeons who also took part in the surgical treatment. YR and MM participated in decision-making for the operation. MT, NS, AT, TM, MG and TY were in charge of follow-up. SY provided pathological diagnosis. MT wrote the manuscript. All authors read and approved the final manuscript.

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