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【 CASE REPORT 】

Successful Control of Hypercalcemia with Sorafenib, Evocalcet, and Denosumab Combination Therapy for Recurrent Parathyroid Carcinoma

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Abstract:

Parathyroid carcinoma (PC) is a rare type of endocrine cancer. Recurrence and metastasis are common after surgery, and refractory hypercalcemia often leads to a poor prognosis. However, there are currently no specific strategies for PC recurrence. We herein report a 61-year-old Japanese man with metastatic PC who was treated with sorafenib, a multikinase inhibitor. In this case, the serum calcium level was under control for 10 months after the initiation of sorafenib. This case suggests that combination therapy with sorafenib, evocalcet, and denosumab may be an alternative, stronger management option for refractory hypercalcemia in recurrent PC.

Key words: parathyroid carcinoma, primary hyperparathyroidism, hypercalcemia, sorafenib, CDC73

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Introduction

Parathyroid carcinoma (PC) is a rare endocrine cancer, accounting for less than 1% of all cases of primary hyperparathyroidism, with 5- and 10-year overall survival rates of 78-85% and 49-70%, respectively (1-4). Refractory hypercalcemia due to hyperparathyroidism and its complications has a significant impact on the prognosis. *En bloc* resection of the entire tumor with the surrounding tissues during the initial surgery is essential for remission. However, more than 50% of patients with PC develop local recurrence or distant metastasis after surgery, and no specific strategy is available to treat such patients (1). In addition, treatment-resistant hypercalcemia is another major problem and the principal cause of mortality from PC. Indeed, adequate control of hypercalcemia prolongs the survival (2).

Recently, the multikinase inhibitor sorafenib has been reported to be useful in the treatment of metastatic PC (5-8), suggesting that sorafenib may be an option for controlling refractory hypercalcemia and pulmonary metastasis associated with PC. However, only a limited number of sorafenib-treated PC cases have been reported, and the clinical course after the administration of sorafenib remains unclear.

We herein report a patient with metastatic PC who was treated with sorafenib and provide a literature review on the effect of sorafenib on the treatment of PC with refractory hypercalcemia and/or multiorgan metastases.

Case Report

A 61-year-old Japanese man with a 2-month history of thirst, polyuria, polydipsia, and fatigue was admitted to our hospital. He had displayed high alkaline phosphatase levels

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Table 1. Results of the Initial Examination.

WBC	7,280 /μL	(3,300-8,600)	FT3	2.6 pg/mL	(2.1-3.8)
RBC	437×10^4 /μL	(386-492×10^4)	FT4	1.0 ng/dL	(0.8-1.5)
Hb	14.5 g/dL	(11.6-14.2)	TSH	1.72 μU/mL	(0.50-3.00)
Plt	27.8×10^4 /μL	(15.8-34.8×10^4)	Intact PTH	1,153 pg/mL	(10-65)
Alb	3.8 g/dL	(4.1-5.1)	Whole PTH	1,090 pg/mL	(14.9-56.9)
T-Bil	0.4 mg/dL	(0.4-1.5)	$1,25(OH)_2D_3$	64 pg/mL	(20.0-60.0)
AST	33 U/L	(13-30)	BAP	139 ng/mL	(3.7-20.9)
ALT	51 U/L	(7-23)	TRACP-5b	>1,500 mU/dL	(120-420)
LDH	204 U/L	(124-222)	FECa	2.3 %	(2-4)
ALP	1,253 U/L	(106-322)	%TRP	74.9 %	(80-92)
γ-GTP	38 U/L	(9-32)			
BUN	15.0 mg/dL	(8.0-22.0)			
Cre	1.12 mg/dL	(0.46-0.79)			
Na	143 mEq/L	(138-145)			
K	4.0 mEq/L	(3.6-4.8)			
Cl	114 mEq/L	(101-108)			
Ca	12.6 mg/dL	(8.8-10.1)			
P	1.9 mg/dL	(2.7-4.6)			
Mg	0.9 mg/dL	(1.8-3.6)			
FPG	111 mg/dL	(73-109)			
HbA1c	5.7 %	(4.9-6.0)			

WBC: white blood cell, RBC: red blood cell, Hg: hemoglobin, Cre: creatinine, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, FT3: free-triiodothyronine, FT4: free-thyroxine, TSH: thyroid-stimulating hormone, PTH: parathyroid hormone, BAP: bone-specific alkaline phosphatase, TRACP-5b: tartrate-resistant acid phosphatase-5b, EFCa: fractional excretion of calcium, %TRP: %tubular reabsorption of phosphate

for four years. He had a history of gastric ulcers 17 years ago. In addition, he had a history of urinary tract stones and fragile rib fractures that had been diagnosed eight years ago and two years ago, respectively. There was no family history of parathyroid disease or other endocrine disorders.

On an examination, no palpable nodules were noted on the anterior neck. His temperature was 36.8°C, pulse 82 beats/m, and blood pressure 155/98 mmHg. Table 1 shows the results of the laboratory examinations at the first visit to our hospital. The serum levels of albumin-corrected calcium (12.5 mg/dL) and intact parathyroid hormone (PTH) (1,168 pg/mL) were high, indicating primary hyperparathyroidism. In addition, bone-specific alkaline phosphatase (BAP) 139 ng/mL (reference range: 3.7 to 20.9) and tartrate-resistant acid phosphatase (TRACP)-5b >1,500 mU/dL (reference range: 120 to 420) were also markedly elevated, suggesting a high turnover of bone metabolism and the presence of fibrous osteitis. Furthermore, a bone mineral density scan by dual-energy X-ray absorptiometry showed markedly decreased T-scores of -3.8, -2.7, and -4.1 at the lumbar 2-4, femoral neck, and distal 1/3 of the radius, respectively. Neck ultrasonography revealed a 20-mm hypoechoic nodule inferior to the right lobe of the thyroid gland with internal heterogeneity and abundant blood flow (Fig. 1A). Computed tomography (CT) revealed a tumor in the same area (Fig. 1B), and ^{99m}Tc-sestamibi scintigraphy single-photon emission computed tomography (SPECT)/CT fusion imaging revealed the mild accumulation of the radiotracer (Fig. 1C). No obvious distant metastases were found on the CT scan. There were multiple hot spots on the right acetabulum, left iliac bone, and ribs bilaterally on radionuclide bone imaging, suggesting the presence of a brown tumor or multiple bone metastases (Fig. 2).

It was speculated that the right lower parathyroid tumor had induced an extremely high intact PTH level and multiple fibrous osteitis lesions. PC was strongly suspected at the diagnosis because of the irregular shape and tumor's depth-width ratio of approximately 1.0 as well as the presence of fibrous osteitis.

It is very important to perform *en bloc* resection at the time of initial surgery to prevent local recurrence (9, 10). Therefore, the patient underwent *en bloc* resection of the entire tumor and the right lower lobe of the thyroid gland. A pathological examination revealed PC with invasion into the surrounding tissues, including the outside of the parathyroid capsule, vasculature, and nerves. After surgical resection of the tumor, the levels of serum calcium (10.5 to 9.7 mg/dL) and intact PTH (1,034 to 38.2 pg/mL) immediately decreased (Fig. 3). The patient was discharged from the hospital in good condition, and regular medical checkups were performed in the outpatient clinic.

However, nine months after surgery, the serum calcium and intact PTH levels gradually increased. CT revealed multiple pulmonary nodules in both lungs, with no apparent recurrence of the primary tumor. The pulmonary nodules grew larger in a short period of time, and a diagnosis of multiple lung metastases of PC was made (Fig. 4A). No other obvious metastases were observed by CT. Treatment options for

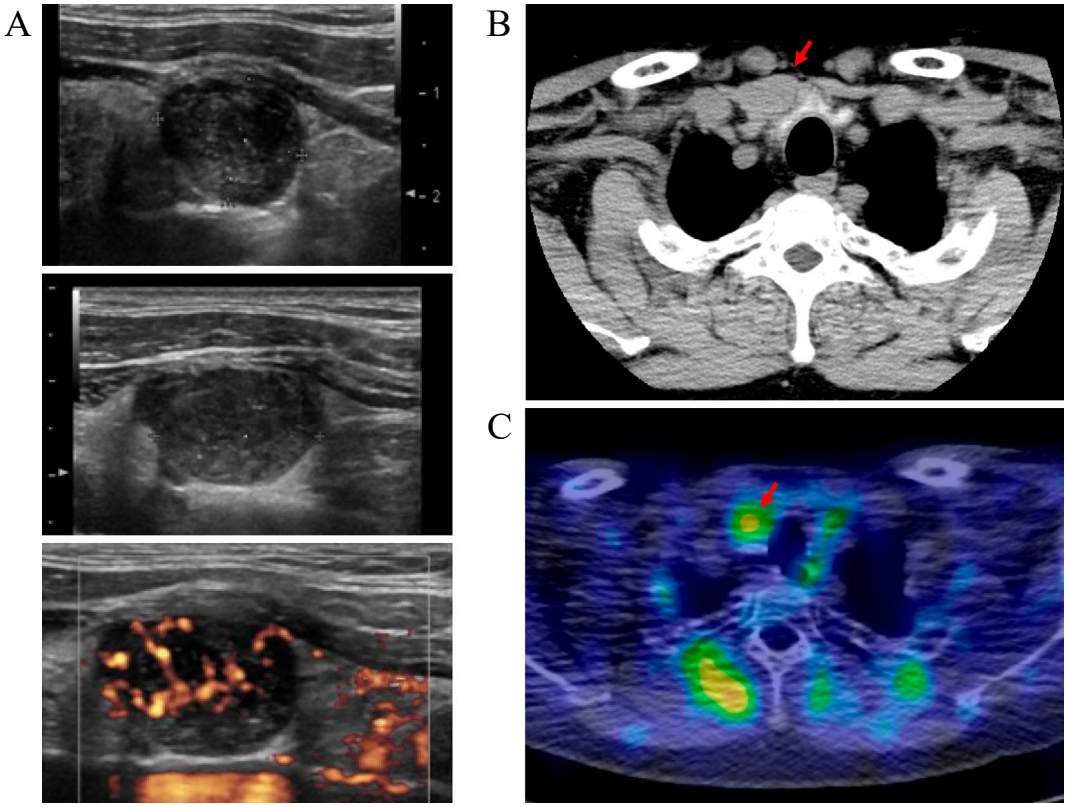

Figure 1. **A: Neck ultrasonography on the first visit showing an approximately 20-mm hypoechoic nodule inferior to the right lobe of the thyroid gland, with internal heterogeneity and abundant blood flow. The nodule in the right lung had shrunk (red arrow), B: CT scan showing a tumor in the same area as on ultrasonography. C: ^{99m}Tc-sestamibiscintigraphy SPECT/CT fusion imaging showing a mild uptake of the radiotracer in the same area. SPECT/CT: single-photon emission computed tomography/computed tomography, CT: computed tomography**

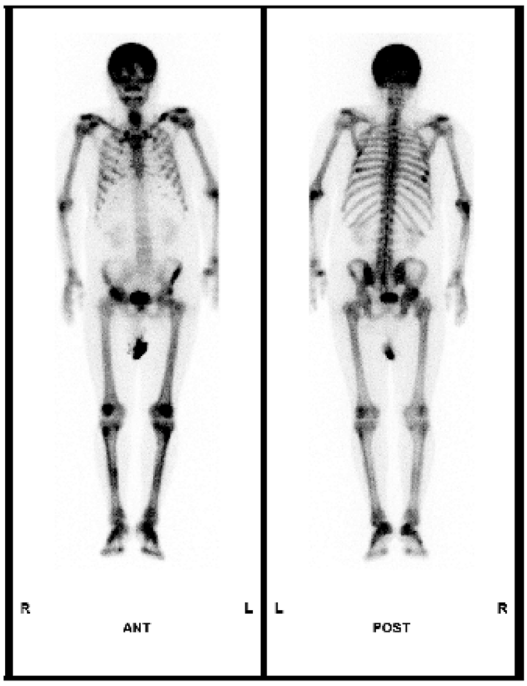

Figure 2. **Radionuclide bone imaging on the first visit. Multiple hot spots were observed on the right acetabulum, left iliac bone, and ribs bilaterally.**

patients with metastatic PC are limited, and no specific strategies are available (2). Surgical resection is primarily recommended for metastatic lesions of PC; however, we were unable to select this approach because of the multiple locations of the metastatic pulmonary nodules in this case. Hypercalcemia progressed despite monthly intravenous zoledronic acid administration and an increased dose of evocalcet, a new calcimimetic, of up to 18 mg/day. We then performed a microsatellite instability test to determine if there was an indication for immune checkpoint inhibitors, but the results were negative. In addition, we used the FoundationOne® CDx gene panel (Foundation Medicine, Cambridge, USA) to consider specific therapies based on genomic profiles. This is a qualitative next-generation sequencing (NGS) technique that analyzes genetic mutation information in genomic DNA extracted from tumor tissue specimens and can be used as an aid in determining the diagnosis and treatment approach (11). We identified a somatic mutation (c.126_131+9delinsCT) in the cell division cycle 73 (CDC73) gene. The CDC73 mutation is a known genomic mutation in the pathogenesis of PC; however, variants identical to those in our case have not been previously reported. At the exon 1/intron 1 junction, we found several reports of deletions (c.126_131+18del24) in somatic muta-

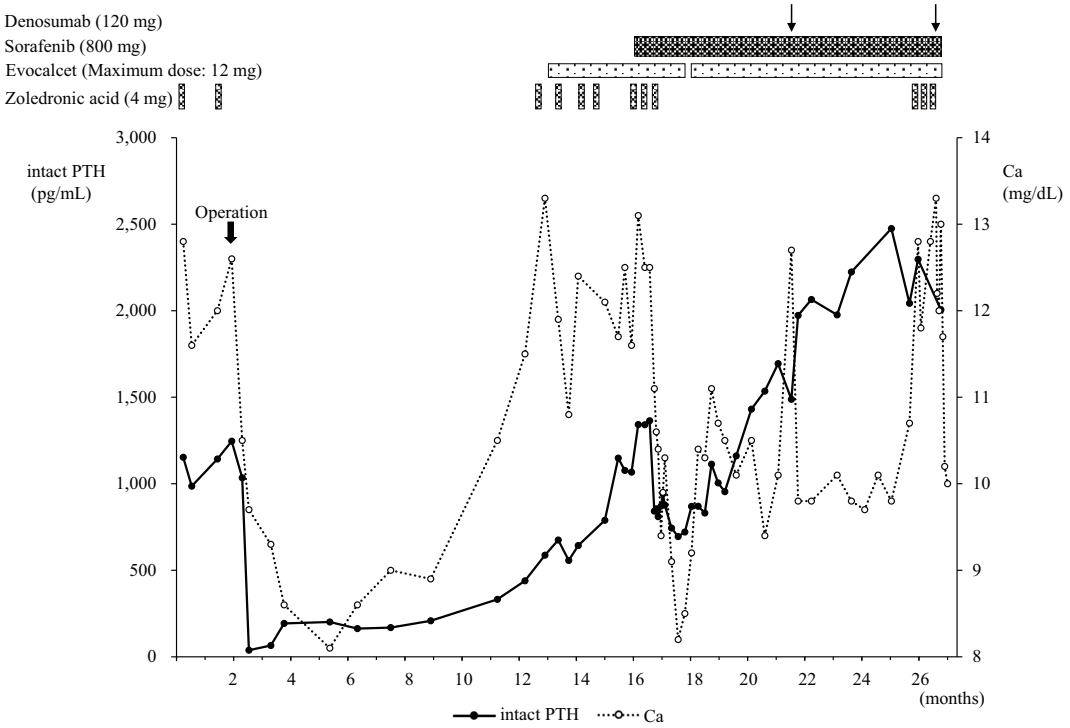

Figure 3. **Summary of the clinical course of the PTH and serum calcium levels from the diagnosis of PC. PC: parathyroid carcinoma, PTH: parathyroid hormone**

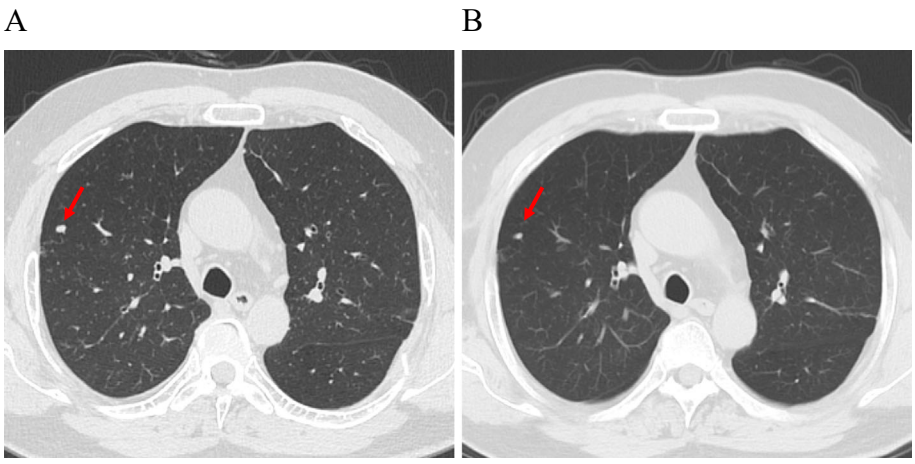

Figure 4. **CT scan before (A) and two months after (B) the administration of sorafenib. The nodule in the right lung had shrunk (red arrow), and other nodules also showed a shrinking trend. CT: computed tomography**

tions but no reports of delins (12-15). However, among germline mutations, there were several reports of the c.131+1G>A (rs587776558) splice site variant (16). In addition, mutations at the exon 1/intron 1 junction were more common than those at other junctions of CDC73 in previous reports. However, no specific targeted therapy or clinical trial has been conducted for CDC73 mutations. Furthermore, no other genetic mutations were viable therapeutic targets in our case.

Erovic et al. reported that the expression of molecular targets of sorafenib, including vascular endothelial growth factor receptor (VEGFR)-2, and platelet-derived growth factor receptor (PDGFR)-α, were increased in PC (17). Immunohistochemical expression of VEGFR-2, but not PDGFR-α, was detected in tumor cells in this case (Fig. 5). Since recent reports have suggested that sorafenib might be effective in the treatment of metastatic PC (5-8), and our case showed the increased expression of sorafenib target molecules in the tumor tissue, we considered the administration of sorafenib. However, sorafenib is not indicated for the treatment of PC in Japan, so we asked the medical safety management department of our hospital to review the off-label use of sorafenib for recurrent PC, and we were able to obtain approval for its use (approval No. 2020-9). Subsequently, we initiated

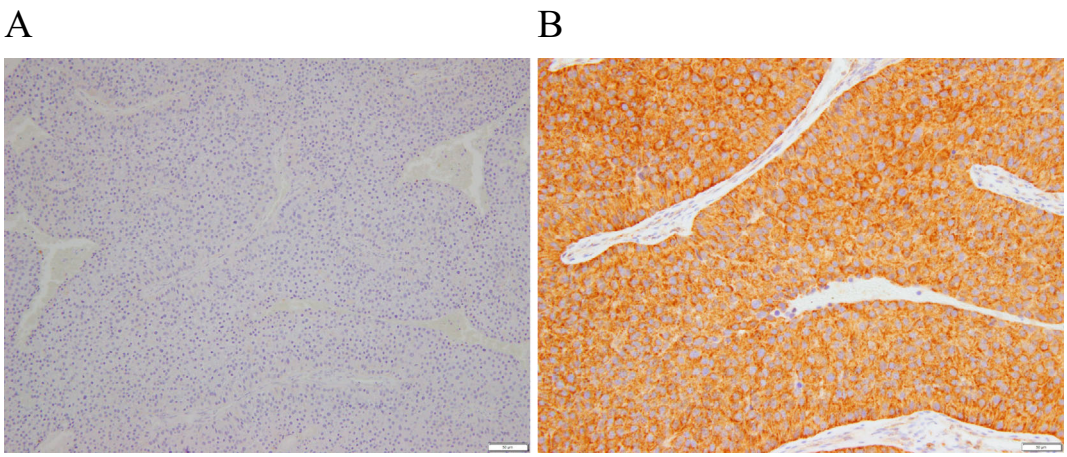

Figure 5. Pathological findings of parathyroid carcinoma. Negative immunostaining for PDGFR-α (A) and diffuse positivity for VEGFR-2 (B) in the tumor cells. An immunohistochemical study was performed using PDGFR-α (monoclonal; Abcam, Cambridge, UK) and VEGFR-2 (monoclonal; Santa Cruz Biotechnology, Dallas, USA). PDGFR: platelet-derived growth factor receptor, VEGFR: vascular endothelial growth factor receptor

molecular targeted therapy with 400 mg sorafenib twice a day.

On the fourth day of sorafenib treatment, there was a dramatic decrease in the levels of both serum calcium [to 11.1 mg/dL (pre-treatment: 12.5 mg/dL)] and intact PTH [to 842 pg/mL (pre-treatment: 1,364 pg/mL)]. Notably, the patient had mild tenderness in the right upper quadrant of the abdomen, elevated pancreatic enzyme levels, and a low CT value of the pancreatic head on abdominal CT. A diagnosis of mild pancreatitis (Common Terminology Criteria for Adverse Events, CTCAE, Grade 2) was made. On day 6, a urinalysis by dipstick showed urine protein 2+ (spot urine protein-to-creatinine ratio of 2.75). The patient's blood pressure was 140/90 mmHg, and amlodipine 2.5 mg/day was initiated for hypertension (Grade 2). The patient also had mild nausea and loss of appetite (Grade 2). After continuing treatment with sorafenib, the proteinuria persisted, but other symptoms improved. On day 16, the serum calcium levels improved to within the reference range (9.4 mg/dL), and the intact PTH level was 871 pg/mL. Treatment with sorafenib was continued. Since the serum calcium levels were well managed, the dose of evocalcet was gradually reduced and it was discontinued on day 43; however, on day 50 of sorafenib treatment, the serum calcium level increased again, and evocalcet was re-introduced.

CT performed two months after the administration of sorafenib showed a mild reduction in the size of the pulmonary nodules (Fig. 4B), and the intact PTH level was maintained at approximately 800 pg/mL at the same time. However, four months after the administration of sorafenib, the intact PTH level was found to be re-elevated, and both the number and size of the pulmonary nodules showed an increasing trend. At five months of sorafenib treatment, the serum calcium level was 12 mg/dL, and the intact PTH level was 1,600 pg/mL. High-dose (120 mg) denosumab was administered to treat refractory hypercalcemia. Denosumab was reported to be effective in refractory hypercalcemia of metastatic PC (18). After the administration of denosumab, the serum calcium levels were well controlled at approximately 10 mg/dL. However, 10 months after the administration of sorafenib, the serum calcium levels increased to 13 mg/dL, and the intact PTH levels were higher than 2,000 pg/mL. Zoledronic acid was administered every week; however, the serum calcium level did not significantly decrease, and denosumab was re-administered. Subsequently, the patient's serum calcium level normalized and sorafenib therapy was continued (Fig. 3). Recently, calcium management has become possible without the need for hospitalization, with maintenance of the activities of daily living.

Discussion

We encountered a case of recurrent PC with a CDC73 mutation. Multiple pulmonary metastases and hypercalcemia appeared shortly after *en bloc* parathyroidectomy. Sorafenib, evocalcet, and denosumab combination therapy may be effective for treatment-resistant hypercalcemia. The patient's serum calcium level was well controlled, and he has stably returned to his activities of daily living for one year after recurrence.

There are few reports of recurrent PC describing the course of calcium and PTH levels after the administration of sorafenib, and this is the first case in Japan to be treated with this multikinase inhibitor. Generally, patients with PC die of uncontrolled severe hypercalcemia rather than direct tumor growth. Therefore, hypercalcemia management is vital in the treatment of PC. However, there have been no reports of effective chemotherapy for inoperable cases (19, 20). Potentially actionable mutations in mTOR/PIK3 pathway genes (ATM, PIK3, TSC, NF1) have been reported in 6/11 (54%) patients with PC (8). Another report also showed alterations in the PI3K/AKT/mTOR pathway in more than 20% of PC

Table 2. Summary of Cases in which Sorafenib was Used for Metastatic PC.

Case	Reference	Age	Sex	Local or parathyroid	Gene mutation	Therapy	Follow up	Outcome (effect of sorafenib)
1	(5)	27	F	Lung	CDC73	Lung surgery Sorafenib	1.8 years	Effective
2	(25)	76	F	Parathyroid, lung	N/A	Sorafenib	1 year	Non
3	(25)	61	F	Parathyroid, lung	N/A	Sorafenib	1 year	Non
4	(25)	64	F	Parathyroid, lymph node, lung, liver, bone	N/A	Radiation therapy, Chemotherapy Sorafenib	3 months	Non
5	(6)	63	M	Lung	None	Denosumab Sorafenib	3 months	Effective
6	(7)	41	M	Lymph node, lung, liver, bone, peritoneum	N/A	Operation, Radiation therapy Chemotherapy Bisphosphonate, Denosumab Sorafenib>>Everolimus	N/A	Non
7	(8)	57	M	Parathyroid, lung	CDC73 KDM5C CTNNB1	Lung surgery, Cinacalcet Bisphosphonate Sorafenib>>Lenvatinib	4.6 years	Effective
Our case	Our case	61	M	Lung	CDC73	Evocalcet, Bisphosphonate Denosumab Sorafenib	1 year	Effective

PC: parathyroid carcinoma, N/A: not available, *: unpublished observation

cases (21, 22). Therefore, we investigated druggable gene mutations with the consent of the patient to determine whether or not treatment based on genetic profiling could be performed. In our case, the FoundationOne® CDx NGS panels showed a mutation in the CDC73 gene, but there have been no reports of therapies targeting this particular gene. CDC73 gene mutations have also been detected in patients with hyperparathyroidism-jaw tumor (HPT-JT) syndrome and in 20-29% of individuals with apparently sporadic PC (23).

Based on reports of successful treatment of metastatic PC with sorafenib, we started sorafenib therapy in this case and confirmed its remarkable efficacy in controlling refractory hypercalcemia and metastasis for several months. However, the mechanism underlying the antitumor effect of sorafenib on metastatic PC remains unclear. Anatomically, the parathyroid glands are well-vascularized organs; therefore, PC is prone to hematogenous metastasis to multiple organs. Sorafenib inhibits tumor angiogenesis by inhibiting the tyrosine kinase activity of VEGFR and PDGFR in vascular endothelial cells. Erovic et al. reported that 86% of PCs showed VEGF overexpression, and PDGFR-α, PDGFR-β, and mTOR were found in 90%, 72%, and 57% of PC cells, respectively (17). These findings suggest that molecular-targeted drugs, such as sunitinib, bevacizumab, pazopanib, and everolimus, may have therapeutic value for the tumor itself (24). In the present case, the dissected tumor was positive for VEGFR-2 and negative for PDGFR-α. These results suggest that VEGFR-thyrosine kinase inhibitor (TKIs), such as sorafenib or sunitinib, may be effective for PC. During sorafenib treatment, serum calcium and intact PTH levels re-elevated; however, the growth of metastatic lesions was somewhat controlled, suggesting the contribution of the anti-angiogenic effect of sorafenib.

Table 2 summarizes cases of metastatic PC treated with sorafenib (5-8, 25). Case 1 showed a CDC73 gene mutation and lung metastases, similar to our case. That patient underwent surgery to remove the pulmonary metastases, but the serum calcium and PTH levels gradually increased. Subsequently, sorafenib was introduced to control the metastases and decrease the calcium and PTH levels. Sorafenib was effective in Cases 2, 3, and 5 for three months; however, in Cases 4 and 6, sorafenib was introduced after chemotherapy (Case 4: carboplatin-paclitaxel → capesitabine; Case 6: capesitabine-temozolomide → cisplatin-etoposide → investigational product) and radiotherapy in patients who had multiple organ metastases to the lungs, bones, and liver and was ultimately ineffective. Case 7 was a patient with HPT-JT syndrome who had a pathogenic somatic mutation in CDC 73. Somatic mutations in the KDM5C gene were also identified in this case. Sunitinib, an angiogenesis inhibitor that inhibits VEGF and PDGF receptors, has been reported to be effective in patients with metastatic renal cell carcinoma with a KDM5C mutation (26). Therefore, sorafenib, an anti-angiogenic multi-targeted tyrosine kinase inhibitor with a target profile similar to that of sunitinib, was used. The antitumor effect of sorafenib was temporary, but after switching to lenvatinib, hypercalcemia and metastasis were successfully controlled for 20 months in Case 7. While genetic testing has been performed in a few cases, the expression of TKI target molecules in the tumor was not investigated in Cases 1-7, so the relationship between their expression rate and the response rate to TKIs is unclear. Based on previous reports, sorafenib may be effective in patients without multiorgan metastases; however, due to the small number of cases and short follow-up duration, only limited information is available. Why sorafenib may be more effective in cases of single organ metastasis than multiple organ metastases is

unclear. Cancer metastasis is generally associated with epithelial-mesenchymal transition (EMT), which is associated with multi-drug resistance through the induction of ABC transporters (27). Fendrich et al. reported that the loss of the epithelial marker E-cadherin was associated with the distinct expression of EMT transcriptional factors snail and twist in PC compared to parathyroid adenoma or hyperplasia (28). Therefore, PC with EMT-associated distant metastasis would have a compromised response to any chemotherapy. Taken together, the early administration of sorafenib may be a viable treatment option when pathological or serological findings suggest tumor persistence or recurrence.

Calcimimetics are effective for the management of hypercalcemia in inoperable PC. Silverberg et al. reported that cinacalcet reduced serum calcium levels by more than 1.0 mg/dL in ≥62% of PC cases (29). Recently, in a Japanese phase 3 trial, evocalcet was reported to have long-term effectiveness in reducing serum calcium levels and to be safe in patients with primary hyperparathyroidism (30). Haven et al. reported that the calcium-sensing receptor (CaSR) expression is decreased or absent in PC, and the suppression of CaSR is well correlated with a high Ki-67 proliferation index (31). Recently, a retrospective study from Japan suggested that cinacalcet reduces the size of parathyroid adenomas in patients with PHPT (32). A similar phenomenon has been observed in secondary hyperparathyroidism due to parathyroid hyperplasia (33). We demonstrated a significant correlation between the Ki-67 score and CaSR suppression in patients with chronic renal failure and secondary hyperparathyroidism (34). In the present case, treatment with evocalcet did not reduce the size of the PC lung metastases. However, the timing of intact PTH re-elevation, while the patient was on the treatment with sorafenib, was somewhat linked with evocalcet cessation. Re-introduction of evocalcet did not reduce the intact PTH level but was effective in lowering calcium levels; however, whether evocalcet cessation drove the induction of PC activation or intact PTH re-elevation is unclear.

In our case, serum calcium levels were well controlled without bisphosphonate despite the elevated trend of intact PTH levels for several months following the administration of sorafenib (approximately 21 months; Fig. 3), suggesting the effect of the combination of sorafenib with evocalcet and denosumab. Regarding the direct effect of TKIs on bone, Murray et al. elegantly reported that sunitinib, a similar TKI to sorafenib, inhibited the osteoclast development and function mediated by macrophage colony-stimulating factor (M-CSF), a differentiating factor for osteoclasts (35). Furthermore, sorafenib decreased the urinary levels of N-terminal cross-linking telopeptide of type I collagen (NTx), a bone resorption marker, in renal cell carcinoma with bone metastasis (36). In the present case, the combination of sorafenib and denosumab displayed strong inhibitory effects against osteoclast-induced bone resorption, subsequently enabling calcium management for recurrent PC.

In conclusion, we herein report a case of metastatic PC that was treated with sorafenib. The clinical course of this case indicates that sorafenib is an effective treatment for refractory hypercalcemia and multiple lung metastases in patients with PC. Combination therapy with sorafenib, evocalcet, and denosumab may be an alternative, strong management option for hypercalcemia in recurrent PC.

Written informed consent for the publications of their clinical details and clinical images was obtained from the patients. A copy of the consent form is available for review by the Editors.

The authors state that they have no Conflict of Interest (COI).

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