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Case Report

Successful Multimodal Treatment of Locally Advanced Parathyroid Carcinoma

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Abstract

Parathyroid carcinoma is a rare endocrine malignancy for which the primary treatment is surgery; however, 50% of the patients develop local recurrence or distant metastases. No consensus exists on the standard treatment for metastatic parathyroid cancer. Here we report a case of a 41-year-old male with inoperable locally advanced parathyroid carcinoma who was successfully treated with multimodal therapy including radiofrequency ablation (RFA), external beam radiation therapy (EBRT) to the neck, and sorafenib. Eleven months after initiating sorafenib, serum calcium levels were normal, and both the intact PTH level and the size of metastatic lesion remained stable; thus, we decided to discontinue sorafenib. After discontinuation, the disease remained stable for 18 months and continues to be so. Hence, clinicians can consider multimodal treatment with RFA, EBRT, and sorafenib as a treatment option for locally advanced parathyroid carcinoma.

Key Words: parathyroid carcinoma, multimodal treatment, hypercalcemia

Introduction

Parathyroid carcinoma is an extremely rare endocrine malignancy, comprising only 0.005% of all cancers [1, 2]. The primary treatment for parathyroid carcinoma is surgery; however, 50% of the patients develop local recurrence or distant metastases [1]. No consensus exists on the standard treatment for patients with recurrent or metastatic parathyroid carcinoma when it is inoperable. Patients with recurrent or metastatic parathyroid carcinoma often suffer from severe hypercalcemia, which is the main cause of mortality and morbidity. We report a case of inoperable locally advanced parathyroid carcinoma that was successfully treated with a multimodal treatment including radiofrequency ablation (RFA), external beam radiation therapy (EBRT), and sorafenib.

Case Presentation

A 41-year-old male presented to the endocrinology clinic with a palpable neck mass and a weight loss of 7 kg over the past 2 months. He had no personal or family history of endocrine disorders.

Diagnostic Assessment

Neck ultrasonography (US) showed multiple low-suspicion thyroid nodules sized up to 3.9 cm located at the posterior aspect of the thyroid with 2 large malignant-looking lymph nodes (LNs) (Fig. 1A-D). Neck computed tomography (CT) imaging showed a 4.5-cm extrathyroidal mass in the left visceral space and multiple enlarged necrotic LNs in the left side of the neck at level 2 and 3 (Fig. 1E). The initial serum calcium level was 16.1 mg/dL (4.02 mmol/L; reference range, 8.6-10.2 mg/dL), and the serum intact PTH (i-PTH) level was 2045 pg/mL (2045 ng/L; reference range, 10-57 pg/mL). Parathyroid single photon emission CT/CT imaging showed increased uptake in the same areas as observed on CT. Parathyroid carcinoma with metastatic LNs was strongly suspected. There was no evidence of bone metastases on the technetium-99m-hydroxydiphosphonate whole-body bone scan.

Treatment

The patient underwent initial en bloc resection including left hemi-thyroidectomy with modified radical neck dissection. Parathyroid carcinoma with metastatic LNs was confirmed by pathological examination, revealing parathyroid carcinoma involvement of the left thyroid parenchyma, extensive capsular invasion, and lymphatic invasion. Out of 27 LNs examined, 3 were positive for metastasis with a maximal diameter of 2.7 cm. The postoperative serum calcium and i-PTH levels were 9.3 mg/dL (2.32 mmol/L) and 10.4 pg/mL (10.4 ng/L), respectively (Fig. 2). Regular follow-up was

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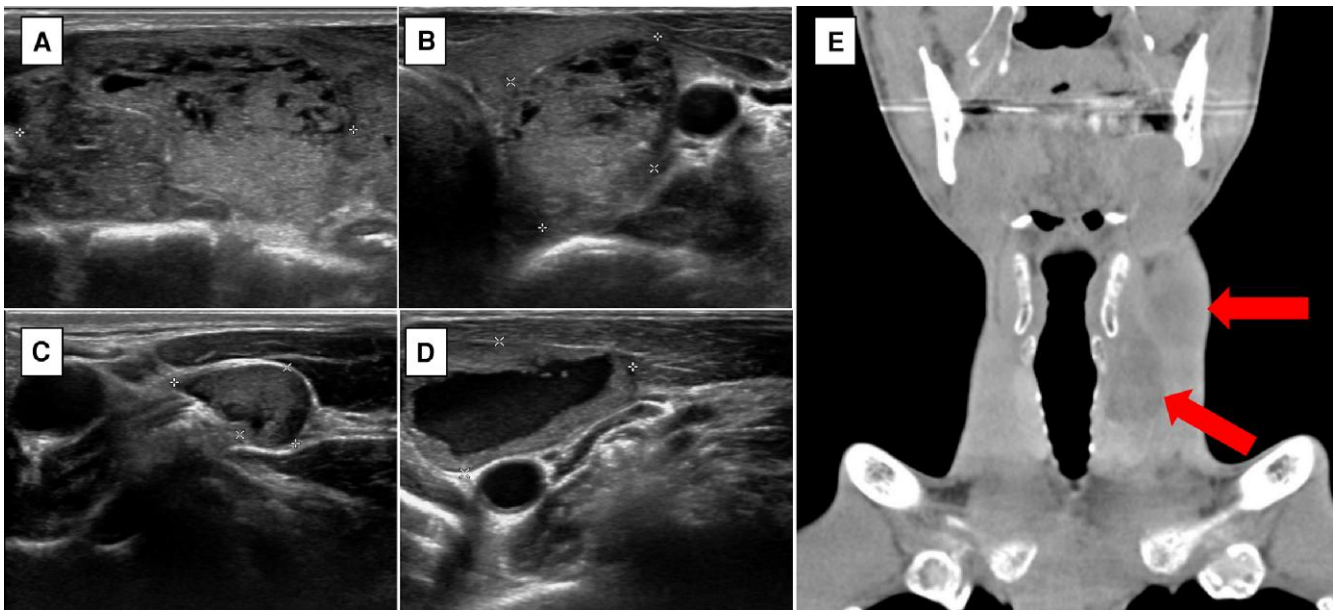

Figure 1. Neck US and CT at the initial presentation. (A, B) Thyroid nodule in the left lobe and left upper pole. (C, D) Malignant lymph nodes in the left side of neck at levels 2 and 3. (E) Neck CT showing masses in the same area as the neck US.

Abbreviations: CT, computed tomography; US, ultrasound.

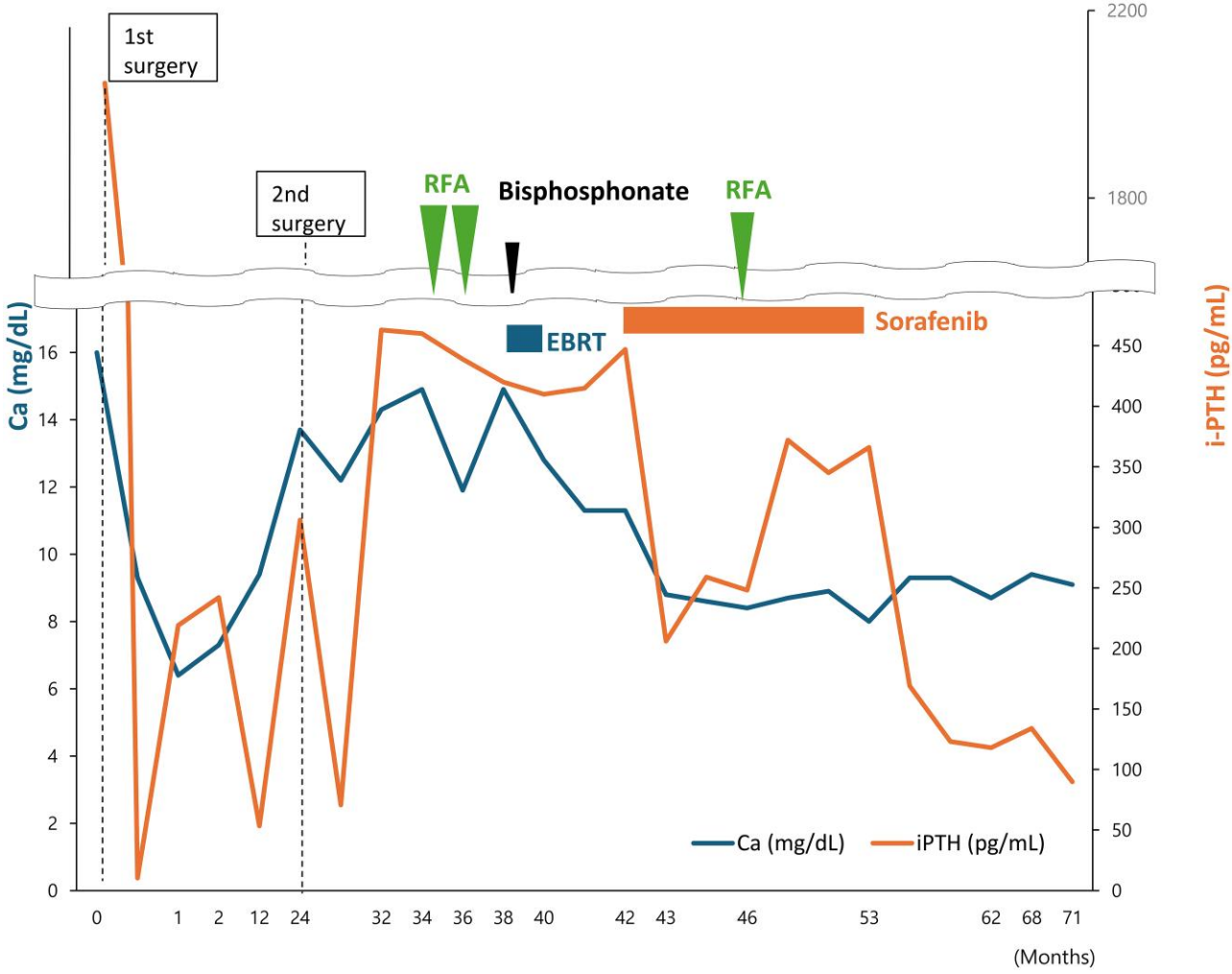

Figure 2. Serum calcium and intact PTH changes during treatment. First surgery: left hemi-thyroidectomy with modified radical neck dissection. Second surgery: selective neck LN dissection.

Abbreviations: EBRT: external beam radiation therapy; LN, lymph node; RFA: radiofrequency ablation.

done, including neck US, blood chemistry, and i-PTH measurements.

Two years after initial surgery, serum calcium and i-PTH levels increased to 13.7 mg/dL (3.42 mmol/L) and 306 pg/mL (306 ng/L), respectively. Imaging studies confirmed parathyroid carcinoma recurrence in the left neck LNs. Therefore, the patient underwent additional selective neck LN dissection. The postoperative serum calcium and i-PTH levels were 12.2 mg/dL (3.04 mmol/L) and 70.8 pg/mL (70.8 ng/L), respectively. However, 6 months after the additional surgery, multiple recurrent tumors were detected on the left thyroid operation bed and lateral neck area with suspicion of esophagus invasion in the neck US. No distant metastases were found on the F-18 fluorodeoxyglucose positron emission tomography/CT scan, apart from the recurrent tumor observed on the neck US. Multiple recurrent lesions suspected of esophagus invasion were detected; we deemed that complete resection would be difficult even with extensive surgery. RFA was planned to treat the recurrent tumors; however, since 1 of the tumors in the left thyroid operation bed was suspected of possibly involving the esophagus (Fig. 3A), complete ablation of the tumor might not have been feasible. We planned additional EBRT to neck with a total dose of 65 Gy following RFA. Intravenous pamidronate was given 3 times during EBRT to control hypercalcemia. Due to impaired kidney function (estimated glomerular filtration rate 44 mL/min/1.73 m^2), the pamidronate dose was reduced from 90 to 45 mg.

Two months following RFA, EBRT, and intravenous bisphosphonate administration, the serum calcium level remained at 11.3 mg/dL (2.82 mmol/L), whereas the i-PTH level gradually increased to 447 pg/mL (447 ng/L). The neck US and CT showed an increase in size of the ablated tumor in the left thyroid operation bed and metastatic LNs in left lateral neck, with residual vascularization on these lesions. Given these findings, we decided to start sorafenib at a dose of 400 mg twice daily.

Outcome and Follow-up

After 1 month of sorafenib treatment, serum calcium and i-PTH levels decreased to 8.8 mg/dL (2.2 mmol/L) and 206 pg/mL (206 ng/L), respectively. Nonetheless, i-PTH levels decreased only slightly and remained elevated. Follow-up imaging at 2 months showed a partial response according to the Response Evaluation Criteria in Solid Tumors version 1.1 [3] (Fig. 3B), but residual lesions remained. We planned additional RFA to treat the residual lesions. Two additional RFAs were performed 5 months after sorafenib initiation.

The patient tolerated the sorafenib treatment, with the main adverse events being hand-foot syndrome (Common Terminology Criteria for Adverse Events grade 2), hypertension (grade 3), and diarrhea (grade 1) [4]. Five months after starting sorafenib, serum calcium levels dropped to 7.4 mg/dL (1.85 mmol/L) with no significant change in i-PTH levels. Due to hypocalcemia, the sorafenib dose was reduced from 800 to 600 mg per day, after which the hypocalcemia improved from 7.4 mg/dL (1.85 mmol/L) to 8.7 mg/dL (2.17 mmol/L).

Eleven months after initiating sorafenib, serum calcium was within normal reference ranges, i-PTH decreased and remained approximately 200 pg/mL (200 ng/L), and no gross change was observed in the target lesions on the follow-up

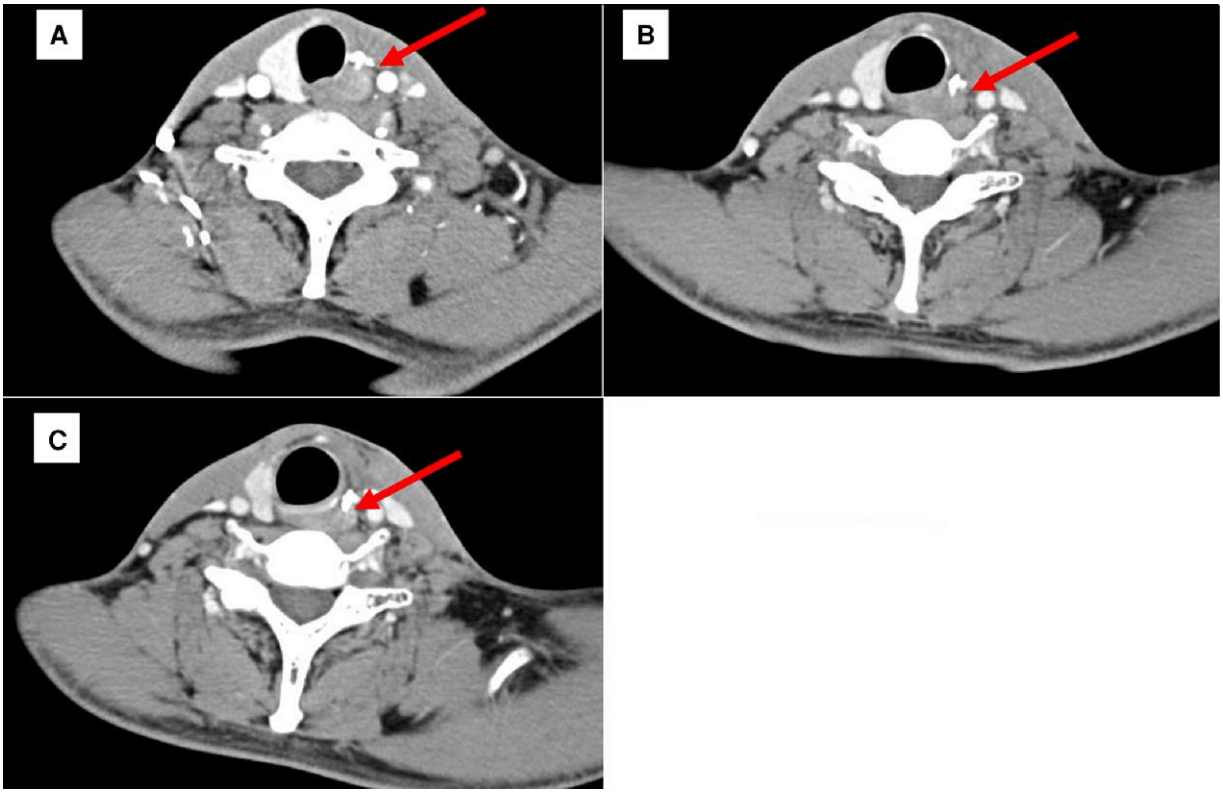

Figure 3. Neck computed tomography image of the recurrent tumor in the left thyroid operation bed. (A) A recurrent tumor was observed in the left thyroid operation bed 6 months after the second surgery. (B) The tumor size decreased after 2 months of sorafenib treatment. Radiofrequency ablation and external beam radiation therapy were performed before sorafenib initiation. (C) The tumor size remained stable after 11 months of sorafenib treatment.

Table 1. Review of previous studies on the treatment of metastatic parathyroid cancer

Case	Ref	Age	Sex	Disease extent	Treatment	Outcomes
1	[6]	61	M	PC with multiple lung metastases	Surgery, denosumab, evocalcet, zoledronic acid, sorafenib	Effective
2	[11]	27	F	PC with multiple lung metastases	Surgery, lung resection, zoledronic acid	Effective
3	[8]	63	M	Intrathyroidal PC with multiple lung metastases	Surgery, denosumab, sorafenib	Effective
4	[9]	61	M	PC with lung metastases	Surgery, denosumab, zoledronic acid, sorafenib	Not effective
5	[9]	41	M	PC with liver, skeletal, lung, peritoneum, lymph node metastases	Surgery, resection of mediastinal mass, manubrium, clavicular head, sternum, and first rib, EBRT, zoledronic acid, capecitabine-temozolomide, etoposide-cisplatin, sorafenib, denosumab, zoledronic acid, everolimus	Not effective
6	[10]	61	F	PC with pleural metastases	Surgery, radiation therapy, evocalcet, denosumab, sorafenib, lenvatinib	Not effective

Abbreviations: EBRT, external beam radiation treatment; LN, lymph node; PC, parathyroid carcinoma.

imaging. Since the biochemical parameters were stabilizing and considering that EBRT and RFA had already been completed, we decided to discontinue sorafenib and wait for the delayed effects of the previous treatments. Over the past 18 months of follow-up, no significant changes were observed in serum calcium levels and tumor size, but i-PTH levels continued to decrease to 89.9 pg/mL (89.9 ng/L).

Discussion

Due to its rarity and unpredictable course, no consensus exists on the treatment of inoperable metastatic or recurrent parathyroid carcinoma. Patients often suffer from severe hypercalcemia, which is the main cause of mortality and morbidity. Controlling hypercalcemia is the major challenge in managing inoperable parathyroid carcinoma. Intravenous bisphosphonate or denosumab are frequently used for managing hypercalcemia in patients with parathyroid carcinoma, but they are often refractory in most cases. Cinacalcet can be considered for hypercalcemia that is refractory to bisphosphonates or denosumab [5]. However, cinacalcet is not approved for the management of hypercalcemia associated with parathyroid carcinoma under the Korean health insurance system, and thus, we were unable to administer cinacalcet in this case.

In general, radiotherapy, chemotherapy, and immunotherapy have shown disappointing results in parathyroid carcinoma. Few reports about the treatment for distant metastatic parathyroid carcinoma are shown (Table 1) [6-11]. Combination therapy consisting of radiation therapy, sorafenib, and denosumab or bisphosphonate was used in most cases, though only some showed effectiveness. Our case was unique because the patient had only local metastasis, whereas patients in previous case reports had distant metastases and because of integrating RFA into the treatment for local tumor control. We successfully controlled hypercalcemia from locally advanced parathyroid cancer with multimodal therapy.

There are no reports about using RFA in parathyroid carcinoma; however, it has been used in recurrent thyroid cancer and parathyroid adenoma for patients who are not suitable for surgery. RFA has shown effectiveness in reducing the volume of tumors or adenomas and normalizing biochemical markers [12]. Since our patient had only local metastasis at the thyroid operation bed and in adjacent LNs, we tried RFA for locoregional control.

However, serum calcium and i-PTH level remained elevated even after the complete ablation of gross metastatic lesions, indicating that RFA alone was insufficient for disease control. Adjuvant EBRT was effective in preventing the progression of local recurrence, suggesting potential benefit in controlling locoregional parathyroid carcinoma [13, 14]. Thus, additional EBRT was applied. Although surgery, RFA, and EBRT were performed to manage the recurred parathyroid carcinoma, hypercalcemia could not be effectively controlled. Sorafenib treatment was initiated.

Sorafenib is a tyrosine kinase inhibitor that blocks tumor cell proliferation and inhibits angiogenesis by targeting vascular endothelial growth factor and platelet-derived growth factor receptors. The exact mechanism by which sorafenib exerts its effects in parathyroid carcinoma remains unclear. However, it may be related to the well-vascularized nature of the parathyroid glands and the overexpression of vascular endothelial growth factor in parathyroid cancers [15, 16]. Additionally, tyrosine kinase inhibitors not only have an antiangiogenic effect but may also inhibit bone resorption in parathyroid carcinoma [17]. One month after initiating sorafenib, the serum calcium level was normalized. This can be regarded as the effect of sorafenib treatment or as an untargeted side effect, considering the event of hypocalcemia during the 800 mg daily treatment. After 11 months of sorafenib treatment, both the tumor extent and biochemical parameters remained stable, and we decided to stop sorafenib. The continuing decrease in serum i-PTH levels following sorafenib discontinuation suggests a delayed effect of EBRT or RFA. Sorafenib could have played a role as a bridging therapy in this situation.

Several genetic mutations are being reported in parathyroid carcinoma, such as *CDC73*, *MEN1*, PI3K/AKT/mTOR pathway gene mutation, and *CCND1* amplification [18]. Currently there are no specific targeted therapies, but targeted genetic therapy could be a promising area for future development.

Inoperable metastatic or recurrent parathyroid carcinoma poses a considerable therapeutic challenge due to the lack of effective treatments. However, this case study suggests that multimodal therapy including RFA, EBRT, and sorafenib may offer potential therapeutic efficacy for patients with inoperable locally advanced parathyroid carcinoma.

Learning Points

- Metastatic parathyroid carcinoma poses a significant therapeutic challenge due to lack of effective treatment.
- Hypercalcemia is a major issue in inoperable and uncontrolled metastatic parathyroid carcinomas.

- Multimodal therapy including RFA, EBRT, and sorafenib could offer a potential therapeutic effect for locally advanced parathyroid carcinoma.

Contributors

All authors made individual contributions to the authorship. N.H.K. contributed to data collection and wrote the manuscript. C.A.K., S.R.C., and K.W.C. were involved in the diagnosis and management of the patient and reviewed the manuscript. W.G.K. was involved in data collection and manuscript editing. M.J.J. contributed to developing the concept, data analysis, and manuscript editing. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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