



# Intrathyroidal Parathyroid Carcinoma in Chronic Kidney Disease: A Case Report and Review of Literature

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## 만성 신장 질환을 동반한 갑상선 내 부갑상선암 1예

김무진 · 송창면 · 태 경 · 지용배

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When parathyroid carcinoma occurs in the thyroid gland, it is very difficult to diagnose before surgery because imaging studies and aspiration cytology cannot distinguish parathyroid carcinoma from thyroid nodule or benign parathyroid disease. A 53-year-old male was referred to our hospital for assessment of hypercalcemia. He had suffered from chronic kidney disease for 13 years. A 2.5×1.5 cm hypoechoic nodule was noted in the left thyroid gland on ultrasonography, and it showed increased uptake on the sestamibi scan. Fine needle aspiration biopsy revealed it to be a parathyroid lesion, which was confirmed by surgery as parathyroid carcinoma completely surrounded by normal thyroid parenchyme. Because ultrasonography and aspiration cytology have only a limited role in distinguishing parathyroid carcinoma from thyroid neoplasm, suspicion of parathyroid carcinoma before or during surgery through careful examination can lead to complete resection at the initial surgery.

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**Key Words** Chronic kidney disease · Hyperparathyroidism · Parathyroid carcinoma · Thyroid nodule.

## Introduction

The diagnosis of parathyroid carcinoma before or during surgery is challenging, especially when the tumor occurs in an unusual location. When this cancer occurs within the thyroid gland, preoperative imaging studies including ultrasound, CT scan, and sestamibi scan have a limited role in distinguishing it from thyroid nodule and benign parathyroid lesion. Even fine needle aspiration biopsy (FNAB) may be confusing because of its cellular similarity to follicular thyroid lesions.<sup>1,2)</sup>

Chronic kidney disease may cause hyperparathyroidism. Physiologic regulation of parathyroid hormone secretion can

cause secondary hyperparathyroidism in response to vitamin D deficiency or hypocalcemia, which are common in patients with chronic kidney disease. Long-term secondary hyperparathyroidism with hypertrophy of the parathyroid gland and decreased function of parathyroid hormone regulation in response to serum calcium level are classified as having tertiary hyperparathyroidism. Therefore, parathyroid lesions in patients with chronic kidney disease are not uncommon and can complicate the diagnosis of parathyroid carcinoma.<sup>3)</sup>

We introduce a case of intrathyroidal parathyroid carcinoma mimicking a thyroid nodule in a 53-year-old male patient with chronic kidney disease, along with a review of the literature.

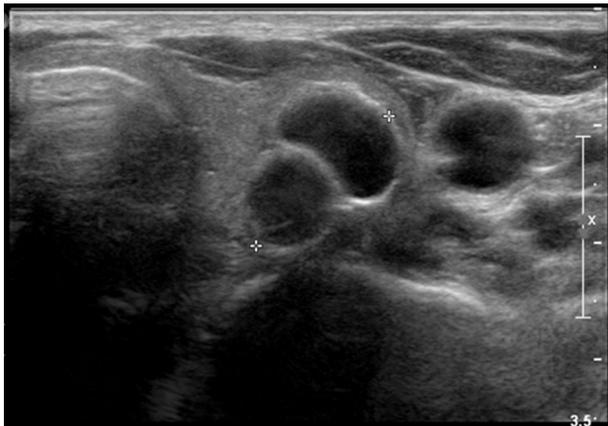
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## Case

A 53-year-old man was referred to our institution with hypercalcemia with hyperparathyroidism. He suffered from chronic fatigue and multiple joint pain. He had diabetes, hypertension, and chronic kidney disease from 13 years ago and was on hemodialysis. A 1.5×1.5 cm firm mass was palpated at the left lobe of the thyroid gland on physical examination, but he reported no problems with his voice or swallowing. Laboratory tests showed an elevated blood urea nitrogen of 65 mg/dL (reference range, 7–20), a creatinine of 10.2 mg/dL (reference range, 0.5–1.4), a serum calcium of 9.7 mg/dL (reference range, 8.2–10.7) and a low phosphate level of 7.0 mg/dL (reference range, 8.4–10.2). Intact parathyroid hormone (PTH) level was markedly elevated at 3115 pg/mL (reference range, 15–55), but thyroid function tests were within normal ranges. Normal 24-hour urinary catecholamines, calcitonin, and pituitary function excluded multiple endocrine neoplasia.

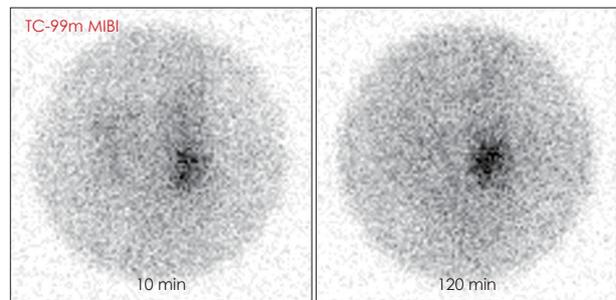
On thyroid neck ultrasonography, a 2.0×1.5 cm lobulated hypoechoic lesion with rim calcification was found in the middle portion of the left thyroid gland (Fig. 1). FNAB was done at this lesion and showed findings consistent with a “parathyroid lesion.” Even though the tumor was located within the thyroid gland, FNAB result and markedly increased PTH level suggested parathyroid tumor. Furthermore, tertiary parathyroid hyperplasia could not be excluded because the patient had chronic kidney disease for a long time and was on hemodialysis. So, we did <sup>99m</sup>Tc-sestamibi parathyroid scan and it showed increased uptake at the left side of the thyroid gland on 10-minute and 2-hour delayed images (Fig. 2).

So, thyroid lobectomy or parathyroidectomy was planned. Because parathyroid gland hyperplasia could not be excluded,



**Fig. 1.** Ultrasonographic findings. A 2×1.5 cm lobulated hypoechoic lesion with rim calcification was found in the middle portion of the left thyroid gland.

ed, we used midline approach by dividing strap muscles for four gland exploration. A 2.5×1.5 cm mass was found in the left lobe of the thyroid gland intraoperatively, which was located within the thyroid gland and surrounding thyroid gland tissue was grossly intact. The left inferior parathyroid gland could not be identified, but the other 3 parathyroid glands were grossly intact. Therefore, a small piece of the left superior parathyroid gland was obtained and was found to be normal parathyroid gland on frozen biopsy. So, left thyroid lobectomy was performed because the tumor was located within the thyroid gland and parathyroid carcinoma was suspected due to markedly high parathyroid hormone level. Several slightly enlarged lymph nodes in the left paratracheal region were harvested (Fig. 3). The thyroid specimen was sent to the pathology department for frozen biopsy and was revealed to be a “parathyroid lesion” confined to the thyroid gland. Permanent biopsy revealed that the 1.8×1.3 cm mass



**Fig. 2.** Sestamibi scan findings. Increased uptake was found at the left side of the thyroid gland on 10- and 120-minute delayed images.



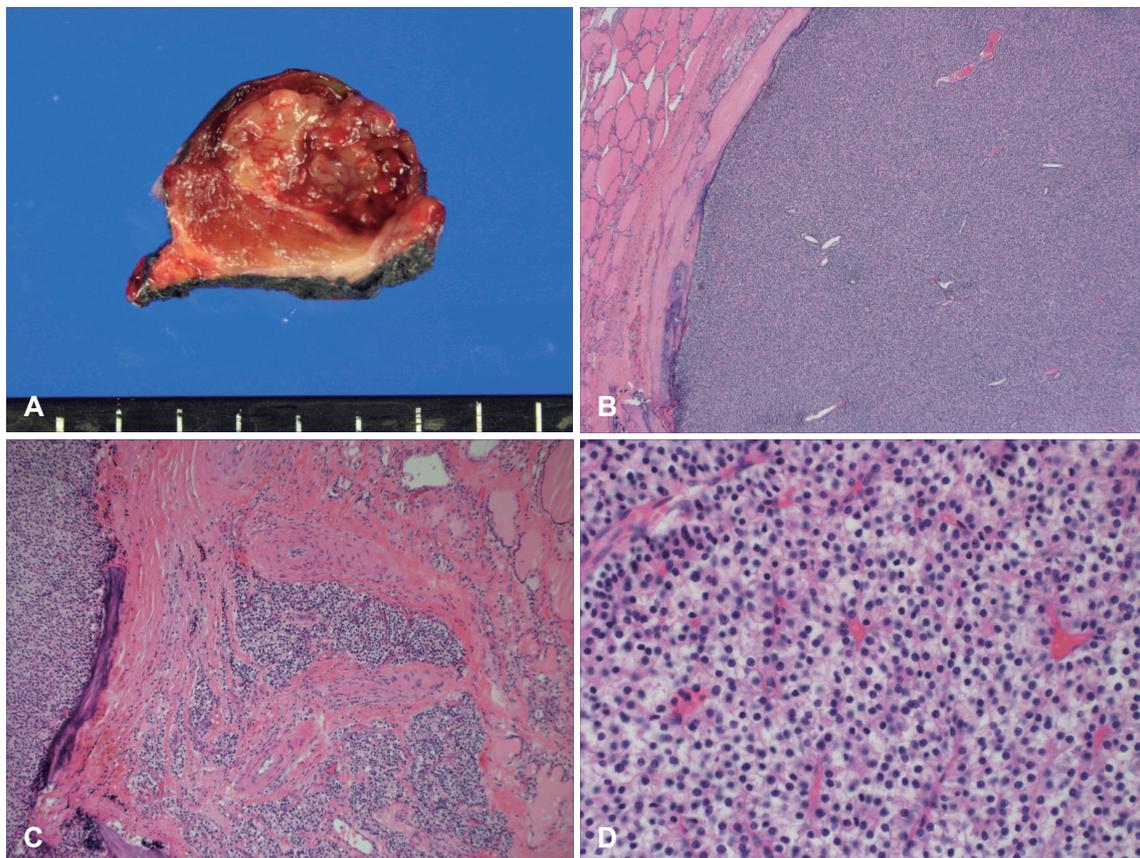
**Fig. 3.** Operative findings. A 2.5×1.5×1.0 cm mass was found in the left lobe of the thyroid gland, and several enlarged lymph nodes were found at the left paratracheal region.

was parathyroid carcinoma completely surrounded by normal thyroid gland tissue. It consisted of chief cells with moderate dysplasia and had invaded into the thyroid gland parenchyma through the tumor capsule (Fig. 4). However, there was no lymph node metastasis. PTH dropped to 75 pg/mL on the first postoperative day. Postoperative care including oral vitamin D and calcium supplements with calcium gluconate injections were provided to prevent hypocalcemic symptoms from hungry bone syndrome. Six days after surgery, the patient was discharged without sequelae. PTH increased to 107 pg/mL during the following year, as determined at an outpatient clinic, but it was 149 pg/mL at the last visit in 3 years after surgery. Moreover, there was no evidence of recurrence on imaging studies including ultrasonography, CT scan, 18F-fluorodeoxyglucose positron emission tomography (PET) scan, and sestamibi scan. Therefore, the patient was followed with medical treatment only, because the increased PTH was attributable to chronic kidney disease rather than recurrence of parathyroid carcinoma.

## Discussion

Parathyroid carcinoma is a very rare cancer that accounts for 0.005% of all cancers. The incidence in patients presenting with primary hyperparathyroidism ranges from less than 0.5% to 3%.<sup>4,5)</sup>

Clinical and laboratory findings may suggest parathyroid carcinoma, however, these findings are nonspecific. Biochemically, the degree of hypercalcemia is more marked in patients with carcinoma (3.75–4.0 mmol/L) than in benign primary hyperparathyroidism (2.7–2.9 mmol/L).<sup>6)</sup> In case of parathyroid carcinoma, the PTH levels are also significantly higher, reported to be greater than 5 to 10 times the normal range. In contrast to benign primary hyperparathyroidism, parathyroid carcinoma patients usually present with palpable mass and end-organ diseases such as osteitis fibrosa cystica, nephrolithiasis and renal and bone disease.<sup>7,8)</sup> FNAB for parathyroid lesions is helpful in identifying or at least suspecting parathyroid origin in unusually located nodules, because imaging studies including ultrasound, CT, and sestamibi scan have



**Fig. 4.** Pathologic findings. The gross cut surface shows a yellowish irregular mass confined to the thyroid gland (A). An encapsulated mass was found in low magnification view (B: H&E stain,  $\times 40$ ). Tumor cells invading into the thyroid gland parenchyma through the capsule (C: H&E stain,  $\times 100$ ). The mass consists of chief cells with moderate dysplasia and is compatible with parathyroid carcinoma (D: H&E stain,  $\times 400$ ). H&E: hematoxylin and eosin.

little role in the diagnosis of parathyroid carcinoma, although they are helpful in localization.

However, differentiating parathyroid carcinoma from adenoma may be impossible on cytology, and parathyroid carcinoma can be confused with several thyroid lesions because they have overlapping cytologic features and some cytomorphologic similarities such as tissue fragments with papillary architecture, epithelial cells arranged in a microfollicular pattern, and colloid-like material in the background.<sup>1,2)</sup> Moreover, the presence of oncocyctic cells and naked nuclei of chief cells in the parathyroid are hard to distinguish from Hurthle cells and lymphocytes, respectively. Therefore, the differential diagnosis should include not only parathyroid adenoma and parathyroid hyperplasia, but also papillary thyroid carcinoma, anaplastic thyroid cancer, and even metastatic renal cell carcinoma.<sup>9)</sup>

Moreover, histologic findings alone are not sufficient for diagnosis of parathyroid carcinoma without malignant histologic features of capsular or neurovascular invasions and/or metastases. The generally accepted histopathologic features of parathyroid carcinoma include trabecular architecture, mitotic figures, thick fibrous bands, and capsular and blood vessel invasion. Immunohistochemical staining for Ki-67, PRAD1/Cyclin D1, p27, and parafibromin is reported to be helpful for diagnosis of parathyroid carcinoma.<sup>10,11)</sup>

Unusual location of the parathyroid also complicates the diagnosis of parathyroid carcinoma. Parathyroid carcinoma can occur anywhere that ectopic parathyroid glands can be located. Several previous studies have reported that parathyroid glands are found in an ectopic location 6% to 22% of the time, and these can be one of the four parathyroid glands or a supernumerary gland. Their locations vary and can include the retro/paraesophageal space, the mediastinum, intrathyroidal sites, the carotid sheath, and in a high undescended cervical position.<sup>12,13)</sup>

The intrathyroidal parathyroid gland is defined as a gland surrounded by thyroid tissue and should be differentiated from subcapsular parathyroid glands. The incidence of intrathyroidal parathyroid gland ranges from 0.5% to 4% and might be higher in patients with hyperparathyroidism.<sup>14-16)</sup> The origin of intrathyroidal parathyroid gland is not fully understood, but it can be either superior or inferior or even supernumerary.

Embryologically, the superior parathyroid gland can be included within the thyroid during the fusion of the ultimobranchial bodies with the median thyroid rudiment.<sup>15)</sup> However, some authors found the intrathyroid parathyroid gland locat-

ed in the lower third of the thyroid lobe, which should be considered as an inferior parathyroid gland.<sup>16)</sup>

To the best of our knowledge, only 14 cases of intrathyroidal parathyroid carcinoma have been reported (Table 1).<sup>17-30)</sup> All of these cases presented with hypercalcemia with or without a neck mass. The PTH level was higher than 200 pg/mL in all cases, and some of them were higher than 1000 pg/mL. Sestamibi scan showed increased uptake in the respective lobe for most cases. FNAB was performed in seven cases, and most of them were misinterpreted as a follicular thyroid lesion or poorly differentiated thyroid carcinoma. Parathyroid lesion was reported in only 2 of these cases, and none of the cases had suspected parathyroid carcinoma on FNAB. Frozen biopsy results were described in 6 cases, and parathyroid carcinoma was suspected in only 2 cases. Oncologic outcomes were mentioned in 12 cases, none of which experienced recurrence, although the follow-up period was too short in most cases (1 month–5 years).

As there is no reliable preoperative diagnostic tool for parathyroid carcinoma, suspicion of parathyroid carcinoma preoperatively or intraoperatively is important for establishing proper surgical strategy. Although laboratory findings alone cannot distinguish parathyroid carcinoma from other hyperfunctioning lesions, PTH level in carcinoma is usually higher than in benign parathyroid lesion. The present case showed a high PTH level of 3115 pg/mL. We could not confirm parathyroid carcinoma even on frozen biopsy in this case, but we removed the entire left thyroid and suspicious lymph nodes.

Patients with parathyroid carcinoma should undergo a comprehensive excision at the time of initial surgery. Complete resection frequently requires excision of the ipsilateral thyroid lobe, overlying strap musculature, and adjacent soft tissues. Because pathologic confirmation of parathyroid carcinoma is not always possible during surgery clinical findings such as preoperative imaging, PTH level or intraoperative finding is important. Because occult lymphatic metastasis is not common, prophylactic neck dissection is not recommended.<sup>4,5,31,32)</sup>

Parathyroid carcinoma is known as a slow-growing and often indolent but progressive tumor. It invades surrounding tissues and metastasizes both hematogeneously and, less commonly, via lymphatics. Complete tumor resection is important for improving prognosis. A higher 5-year survival rate was reported when ipsilateral hemithyroidectomy accompanied the initial resection (90.0% with hemithyroidectomy and 82.5% without hemithyroidectomy).<sup>33)</sup> A national cancer data base study reported 5- and 10-year overall survival rates of 82.3%

**Table 1.** Review of previous reports of intrathyroidal parathyroid carcinoma

Case	Age/sex	Presentation	Past history	PTH level	Tumor location/size	Cytologic diagnosis	Frozen biopsy	Treatment	Outcome, f/u
Ernst et al. <sup>17)</sup>	52/F	Hyperparathyroidism, hypercalcemia	Nephrolithiasis	-	Lt. thyroid/ 2.5 cm	-	-	Thyroid lobectomy	NED, 4 months
Crescenzo et al. <sup>18)</sup>	60/F	Left neck mass, hyperparathyroidism, hypercalcemia	Gastric ulcer, nephrolithiasis	205	Lt. thyroid/ 1.5 cm	Follicular thyroid neoplasm	Parathyroid carcinoma	Thyroid lobectomy, isthmusectomy	NED, 8 months
Kirstein and Ghosh <sup>19)</sup>	74/M	Hyperparathyroidism	CKD, hypertension, CHF, COPD	652	Lt. thyroid/-	-	-	Thyroid lobectomy	-
Schmidt et al. <sup>20)</sup>	76/F	Hyperparathyroidism, hypercalcemia	Asthma, HTN, DM, CAD	580	Rt. sup. thyroid/3.2 cm	-	Parathyroid carcinoma	Total thyroidectomy	NED, 1 year
Hussein et al. <sup>21)</sup>	63/F	Hyperparathyroidism, hypercalcemia, body aches, fatigue, constipation, reflux disease	HTN, nephrolithiasis, depression, renal insufficiency	760	Lt. thyroid/ 6.0 cm	-	-	Thyroid lobectomy	NED, > 1 month
Foppiani et al. <sup>22)</sup>	67/F	Hyperparathyroidism, hypercalcemia, multinodular goiter	Lt. hemithyroidectomy for nodular goiter	721	Rt. thyroid/ 3.0 cm	-	Thyroid lesion with pleomorphism	Total thyroidectomy	NED, 5 years
Temnim et al. <sup>23)</sup>	63/F	Hyperparathyroidism, hypercalcemia	Hypertension, nephrolithiasis	-	Lt. thyroid/ 6.0 cm	-	Benign thyroid tissue	Total thyroidectomy	NED, 2 years
Herrera-Hernández et al. <sup>24)</sup>	14/F	Hyperparathyroidism, hypercalcemia	Polyarthralgia, muscle atrophy, joint deformity	2792	Right thyroid/ 2.5 cm	-	-	Thyroid lobectomy	NED, 18 months
Krujjac et al. <sup>25)</sup>	40/M	Hyperparathyroidism, hypercalcemia	Nephrolithiasis	989	Lt. thyroid/ 3.1 cm	Poorly differentiated thyroid follicular carcinoma	Medullary thyroid carcinoma	Total thyroidectomy, MRND	NED, 10 months
Vila Duckworth et al. <sup>26)</sup>	51/F	Hyperparathyroidism, hypercalcemia	-	579	Rt. Inf. thyroid/ 1.4 cm	Indeterminate for follicular neoplasm	-	Total thyroidectomy, parathyroidectomy	NED, 2.5 years
Lee et al. <sup>27)</sup>	59/F	Hyperparathyroidism, hypercalcemia	MEN type I	248	Rt. thyroid/ 2.1 cm	Follicular lesion	-	Thyroid lobectomy	-

**Table 1.** Review of previous reports of intrathyroidal parathyroid carcinoma (continued)

Case	Age/sex	Presentation	Past history	PTH level	Tumor location/size	Cytologic diagnosis	Frozen biopsy	Treatment	Outcome, f/u
You et al. <sup>28)</sup>	33/F	Hyperparathyroidism, hypercalcemia	Nephrolithiasis	965	Lt. thyroid/6.0 cm, Rt. upper parathyroid gland/0.8 cm	-	-	Total thyroidectomy, upper right parathyroidectomy	-
Tejera Hernández et al. <sup>29)</sup>	25/M	Hyperparathyroidism, hypercalcemia	Osteogenesis imperfecta	800	Rt. thyroid/2.0 cm	Follicular thyroid neoplasm	-	Thyroid lobectomy	NED, 16 months
Balakrishnan et al. <sup>30)</sup>	60/F	Hyperparathyroidism, hypercalcemia	Schizophrenia	1721	Rt. thyroid/3.6 cm	Parathyroid lesion	-	Total thyroidectomy	NED, 6 months
Ji et al. (present case)	53/M	Hyperparathyroidism, hypercalcemia left neck mass	HTN, DM, CKD	3115	Rt. thyroid/1.8 cm	Parathyroid lesion	Parathyroid lesion	Thyroid lobectomy	NED, 3 years

NED: no evidence of disease, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disorder, HTN: hypertension, DM: diabetes mellitus, CKD: chronic kidney disease, CAD: coronary artery disease, Sup.: superior, MEN: multiple endocrine neoplasia, PTH: parathyroid hormone, MRND: modified radical neck dissection

and 66%, respectively.<sup>34)</sup>

In this case, the left inferior parathyroid gland could not be identified during the operation, and a thyroid nodule was reported as a parathyroid lesion on the frozen biopsy. Thyroid lobectomy and left paratracheal lymph node biopsy were performed. Because the tumor was confined to the thyroid gland and parathyroid hormone levels remained stable but high, we followed the patient without adjuvant therapy. During the 3 years of follow-up, PTH increased to around 120 pg/mL due to chronic kidney disease, but there was no evidence of recurrence on imaging studies including ultrasonography, CT scan, PET/CT scan, and sestamibi scan.

In conclusion, parathyroid lesion including carcinoma should be suspected when PTH is substantially increased, although parathyroid carcinoma is uncommon. Clinicians should be aware that masses in unusual locations, even in the thyroid gland, might be parathyroid carcinoma, because parathyroid glands can exist at various ectopic locations. Because there are no reliable preoperative diagnostic tools for parathyroid carcinoma, suspicion of parathyroid carcinoma before or during surgery is important. Suspicion and careful examination can lead to complete resection at the initial surgery, which is important for the best chance of cure.

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