Progression of Secondary to Tertiary Hyperparathyroidism with a Coexisting Parathyroid Adenoma in Stage 3b Chronic Kidney Disease: A Case Report

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ABSTRACT

Tertiary hyperparathyroidism arises when prolonged secondary hyperparathyroidism progresses to autonomous parathyroid hormone secretion with persistent hypercalcemia, most often in chronic kidney disease. Diffuse or nodular multiglandular hyperplasia is the expected pathology; a discrete parathyroid adenoma arising within hyperplastic tissue is uncommon and may be overlooked when imaging is negative early in the disease course.

A 60-year-old man with stage 3b chronic kidney disease and long-standing secondary hyperparathyroidism presented with recurrent hypercalcemia and severe vomiting. Laboratory evaluation confirmed elevated serum calcium and parathyroid hormone. Initial cervical ultrasonography showed no parathyroid enlargement, but repeat imaging demonstrated a progressively enlarging lesion adjacent to the left thyroid lobe. He underwent subtotal parathyroidectomy with bilateral cervical exploration. Histopathology showed multiglandular hyperplasia of the right parathyroid glands together with a distinct encapsulated adenoma arising within hyperplastic left parathyroid tissue. Serum calcium normalized postoperatively.

Keywords: *Hyperparathyroidism, secondary, parathyroid neoplasms, adenoma, parathyroidectomy, renal insufficiency, chronic, hypercalcemia.*

INTRODUCTION

Secondary hyperparathyroidism (SHPT) commonly develops in patients with chronic kidney disease (CKD) as an adaptive response to disturbances in calcium–phosphate homeostasis, impaired vitamin D activation, and reduced responsiveness of the calcium-sensing receptor. Persistent stimulation of the parathyroid glands results in progressive glandular hyperplasia and sustained elevation of parathyroid hormone (PTH) levels.[1]

Although tertiary hyperparathyroidism (THPT) most commonly occurs in patients with advanced CKD, particularly those undergoing dialysis, the coexistence of a distinct parathyroid adenoma within the background of long-standing SHPT is considered rare. Most cases of THPT demonstrate diffuse or nodular hyperplasia rather

than monoclonal neoplastic transformation. The exact prevalence of such coexistence remains unclear, as current evidence is largely limited to case reports and small case series.[1]

With prolonged disease duration, a subset of patients may progress to THPT, a condition characterized by autonomous PTH secretion and persistent hypercalcemia despite correction of the underlying metabolic abnormalities.[1,2] Although multiglandular parathyroid hyperplasia is generally regarded as the typical pathological finding, chronic stimulation may also lead to diverse pathological changes, including nodular transformation and, in rare cases, the development of autonomous parathyroid adenomas.[1,3]

We report a case of THPT developing from long-standing SHPT in a patient with CKD, demonstrating the coexistence of multiglandular hyperplasia and a distinct parathyroid adenoma.

CASE ILLUSTRATION

A 60-year-old man with stage 3b chronic kidney disease (CKD) secondary to diabetic kidney disease presented with a one-day history of persistent postprandial vomiting occurring up to ten episodes per day. These symptoms were suggestive of severe hypercalcemia. There was no history of chest pain, palpitations, muscle cramps, seizures, or respiratory symptoms.

The patient had a long-standing history of secondary hyperparathyroidism (SHPT) associated with CKD and recurrent episodes of hypercalcemia requiring multiple hospitalizations. His medical history was also notable for type 2 diabetes mellitus and hypertension. There was no history of malignancy, chronic liver disease, or other endocrine disorders.

Physical examination revealed an underweight but fully conscious patient with stable vital signs. Neck examination revealed a palpable, firm, well-circumscribed mass measuring approximately 1×2 cm in the left lateral cervical region, without overlying skin changes or significant lymphadenopathy.

Laboratory evaluation revealed severe and persistent hypercalcemia (14.4 mg/dL), hyperphosphatemia (5.02 mg/dL), and hypomagnesemia (1.45 mg/dL). Previous biochemical assessments had demonstrated elevated intact parathyroid hormone (PTH) levels (152 pg/mL) and vitamin D insufficiency. Detailed laboratory findings are summarized in **Table 1**. The chronological progression of biochemical findings, imaging studies, and surgical management is illustrated in **Figure 1**.

To exclude alternative causes of hypercalcemia, serum protein electrophoresis was performed, which showed no evidence of monoclonal gammopathy. Serum parathyroid hormone-related protein (PTHrP) was not measured in this patient. However, the markedly elevated intact PTH level, in conjunction with the clinical history of long-standing SHPT, strongly supported a parathyroid-dependent mechanism of hypercalcemia. In addition, there were no clinical, laboratory, or imaging findings suggestive of an underlying malignancy.

Initial neck ultrasonography did not demonstrate parathyroid enlargement. However, subsequent imaging studies revealed a progressively enlarging lesion adjacent to the left thyroid lobe. Cervical magnetic resonance imaging was performed to further characterize the lesion after inconclusive ultrasonographic findings, demonstrating a dominant left

Table 1. Key biochemical findings during the clinical course.

Parameter	Initial Evaluation	Preoperative	Postoperative	Reference Range
Serum calcium (mg/dL)	14.4	13.4	8.7	8.5 – 10.5
Intact PTH (pg/mL)	152	177	6	15 – 65
Serum phosphate (mg/dL)	5.02	4.76	3.88	2.5 – 4.5
25-hydroxyvitamin D (ng/mL)	26.2	25.5	—	30 – 100
Serum creatinine (mg/dL)	2.19	1.47	1.92	0.5 – 1.2
Estimated GFR (mL/min/1.73 m²)	34	54	39	>60

PTH, parathyroid hormone; GFR, glomerular filtration rate.

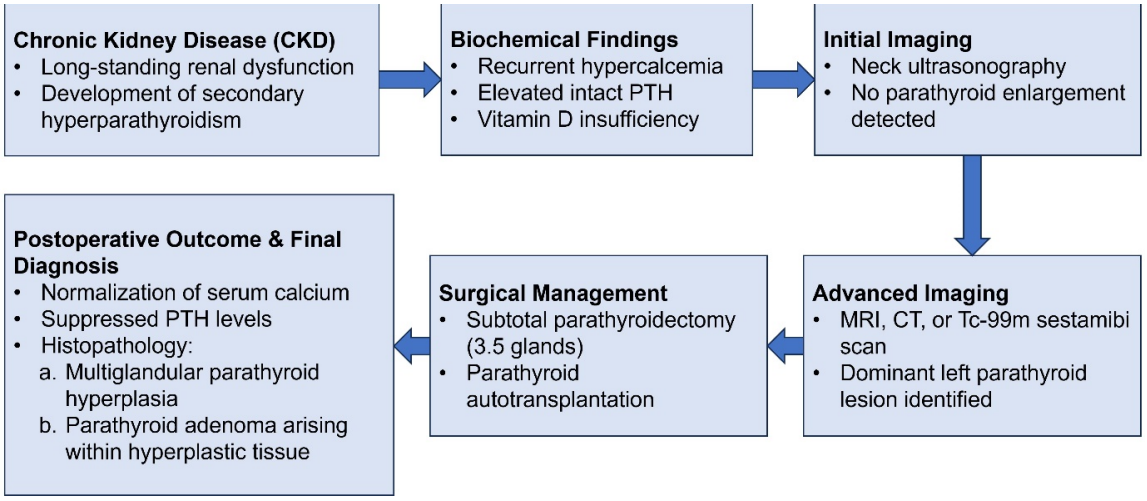


Figure 1. Clinical timeline illustrating the progression from secondary to tertiary hyperparathyroidism, including the evolution of biochemical findings, imaging localization, surgical intervention, and postoperative biochemical remission.

parathyroid lesion (**Figure 2**). This finding was later confirmed by technetium-99m sestamibi scintigraphy and contrast-enhanced computed tomography. Bone mineral density assessment revealed low bone mass without radiographic evidence of brown tumors or metastatic disease.

Because hypercalcemia and elevated PTH levels persisted despite medical management, surgical intervention was considered necessary. The patient underwent a subtotal parathyroidectomy involving the removal of 3.5 parathyroid glands, with bilateral cervical exploration and autotransplantation of parathyroid tissue.

Histopathological examination demonstrated multiglandular parathyroid hyperplasia involving the right superior and inferior parathyroid glands, characterized by diffuse proliferation of chief cells without cytological atypia. In contrast, the left parathyroid gland showed a well-circumscribed, encapsulated lesion composed of proliferating chief cells with eosinophilic cytoplasm and no evidence of capsular, vascular, or perineural invasion. These findings were

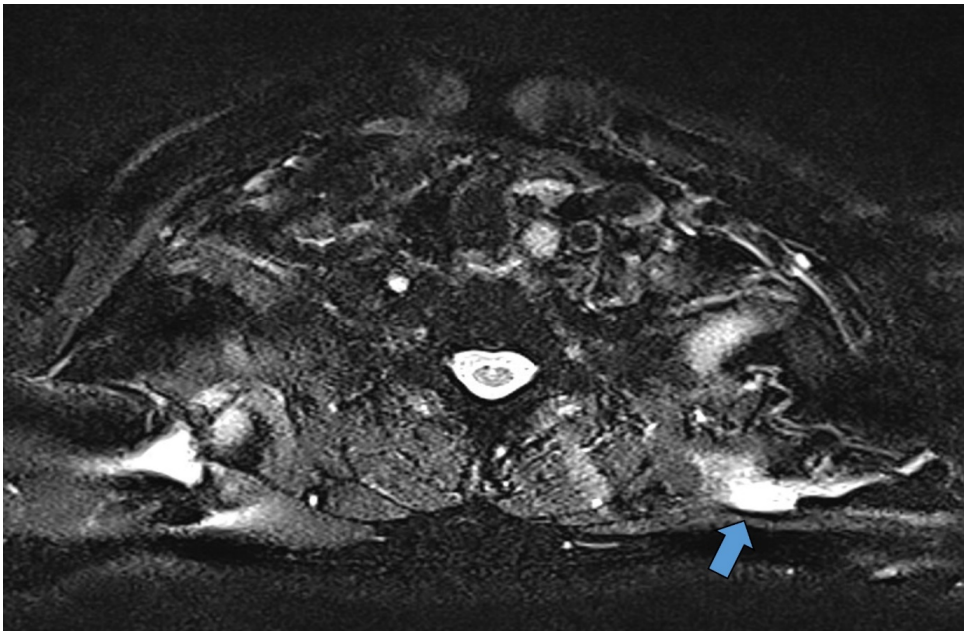


Figure 2. Axial T2-weighted cervical magnetic resonance image demonstrating a hyperintense lesion (arrow) adjacent to the left thyroid lobe, consistent with a parathyroid adenoma.

consistent with a distinct parathyroid adenoma arising within hyperplastic parathyroid tissue (**Figure 3**).

Following surgery, the patient achieved biochemical remission, with serum calcium decreasing to 8.7 mg/dL and PTH levels declining to 6 pg/mL. Clinical symptoms resolved, and a three-month follow-up evaluation showed no recurrence of hypercalcemia.

DISCUSSION

Tertiary hyperparathyroidism (THPT) represents the advanced stage of prolonged secondary hyperparathyroidism (SHPT) and most commonly occurs in patients with chronic kidney disease (CKD). Although THPT typically develops in advanced CKD or dialysis-dependent patients, it may also occur in patients with earlier stages of CKD when SHPT persists over a prolonged period. Persistent stimulation of the parathyroid glands resulting from disturbances in calcium–phosphate metabolism, vitamin D deficiency, and reduced responsiveness of the calcium-sensing receptor leads to progressive parathyroid hyperplasia and sustained elevation of parathyroid hormone (PTH) levels.[1,3,4]

With prolonged disease duration, parathyroid function may become autonomous, resulting in persistent hypercalcemia despite the correction of underlying metabolic abnormalities. This transition from SHPT to THPT represents an important clinical turning point, as patients may become refractory to medical therapy and eventually require surgical intervention.[1,5]

The development of a parathyroid adenoma in the setting of long-standing SHPT is thought to represent a transition from polyclonal hyperplasia to monoclonal proliferation. Chronic stimulation due to hypocalcemia, hyperphosphatemia, and reduced vitamin D activity may promote autonomous growth of parathyroid cells. This process is often accompanied by decreased expression of calcium-sensing receptors and vitamin D receptors, leading to reduced sensitivity to physiological feedback mechanisms. Over time, nodular transformation may occur, and in rare cases, clonal expansion may lead to the formation of a true adenoma within hyperplastic parathyroid tissue.[1,5,6]

Multiglandular parathyroid hyperplasia is generally considered the predominant pathological finding in THPT.[1,6,7] Prolonged stimulation of the parathyroid glands in patients with CKD may lead to progressive structural changes and functional autonomy. Although diffuse hyperplasia is the most commonly reported pattern, heterogeneous pathological involvement can occasionally be observed, including nodular transformation or focal adenomatous lesions. This heterogeneity reflects the complex adaptive response of chronically stimulated parathyroid tissue, highlighting that the pathological spectrum of THPT can vary considerably among patients.

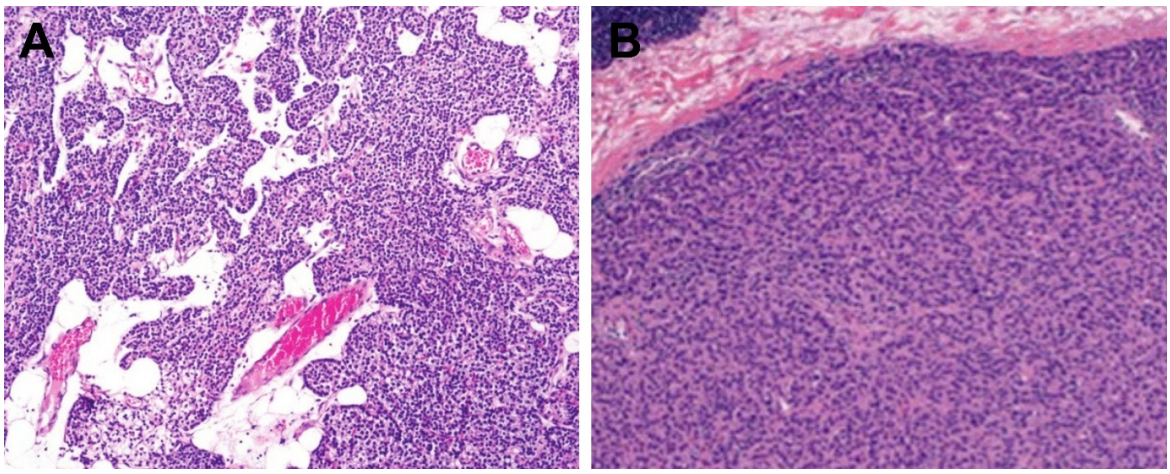


Figure 3. Histopathological findings of the parathyroid glands. (A) Right parathyroid gland demonstrating diffuse chief cell proliferation consistent with parathyroid hyperplasia. (B) Left parathyroid gland demonstrating an encapsulated proliferation of chief cells consistent with parathyroid adenoma (hematoxylin–eosin stain).

In the present case, histopathological examination demonstrated the coexistence of multiglandular parathyroid hyperplasia and a distinct encapsulated adenoma. Diffuse chief cell proliferation was observed in the right parathyroid glands, consistent with hyperplasia, whereas the left gland showed a circumscribed lesion consistent with a parathyroid adenoma. This combination supports the concept that long-standing SHPT may occasionally result in heterogeneous parathyroid pathology.

Reports describing the coexistence of multiglandular parathyroid hyperplasia and a distinct parathyroid adenoma in THPT remain limited, highlighting the rarity of this condition. Most available evidence is derived from isolated case reports and small series, and the true prevalence has not been well established.[1,4]

Distinguishing THPT from primary hyperparathyroidism (PHPT) is clinically important, particularly in patients with CKD, as both conditions may present with elevated PTH levels and hypercalcemia. In PHPT, hypercalcemia typically precedes the elevation of PTH levels, whereas in THPT, hypercalcemia generally develops after prolonged SHPT.[5,8,9] In the present case, the patient had a well-documented history of SHPT related to CKD before the onset of hypercalcemia, supporting the diagnosis of THPT rather than PHPT. Although PTH levels were only moderately elevated, the presence of persistent hypercalcemia in a patient with long-standing SHPT further supported the diagnosis of THPT. Furthermore, histopathological examination demonstrated multiglandular hyperplasia involving multiple parathyroid glands, a finding that is more characteristic of THPT than PHPT.

Imaging studies play an important role in localizing dominant parathyroid lesions; however, their sensitivity may be limited in cases of multiglandular disease. Initial ultrasonography in this case did not detect parathyroid enlargement. Subsequent multimodal imaging, including magnetic resonance imaging, technetium-99m sestamibi scintigraphy, and computed tomography, identified a dominant lesion adjacent to the left thyroid lobe. These findings highlight the importance of repeated and multimodal imaging approaches in patients with persistent or refractory hyperparathyroidism.

Surgical intervention remains the definitive treatment for THPT, particularly in patients with persistent hypercalcemia that is refractory to medical therapy. Subtotal parathyroidectomy with bilateral cervical exploration and selective parathyroid autotransplantation is commonly performed and has been shown to achieve sustained biochemical remission.[3,10] In the present case, this surgical approach led to normalization of serum calcium levels and suppression of PTH levels.

Clinically, the presence of a coexisting adenoma may contribute to resistance to medical therapy, including calcimimetics and vitamin D analogs, and may explain persistent hypercalcemia despite appropriate medical therapy. This condition may necessitate surgical intervention and influence operative planning, particularly regarding the extent of gland exploration and resection. Recognition of this entity is therefore important, as it may impact both therapeutic decision-making and long-term outcomes.[1,10]

This case highlights the importance of considering THPT in patients with CKD who develop persistent hypercalcemia despite medical management. In regions with a high prevalence of CKD, greater awareness of THPT is essential to facilitate timely referral for surgical management. Recognition of this pathological heterogeneity may also influence surgical strategy and postoperative monitoring. This case further supports the concept that long-standing SHPT may give rise to heterogeneous and occasionally monoclonal parathyroid pathology.

CONCLUSION

This case illustrates that tertiary hyperparathyroidism may present with heterogeneous pathological findings, including the coexistence of multiglandular hyperplasia and a distinct parathyroid adenoma. It further highlights the rare possibility of monoclonal adenoma formation within chronically stimulated parathyroid tissue. Recognition of this pathological spectrum is essential for accurate diagnosis and appropriate surgical management

in patients with chronic kidney disease and long-standing secondary hyperparathyroidism.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FUNDING

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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The authors declare that this manuscript is original, has not been previously published, and is not under consideration for publication elsewhere. All authors have read and approved the final manuscript and agree to its submission to Acta Medica Indonesiana (The Indonesian Journal of Internal Medicine).

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