Gazi Med J 2026;37(3):446-449

DOI: http://dx.doi.org/10.12996/gmj.2026.4679

Marked Hypercalcitoninemia without Medullary Thyroid Carcinoma: A Case Report

Medüller Tiroid Karsinomu Olmaksızın Belirgin Hiperkalsitoninemi: Olgu Sunumu

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ABSTRACT

This case report investigates the diagnostic difficulties associated with persistently elevated calcitonin levels in a patient with nodular thyroid disease, where biochemical evidence strongly indicated medullary thyroid carcinoma (MTC), yet histopathological analysis ultimately identified benign nodular hyperplasia with C cell activation.

We describe a 35-year-old male with hypothyroidism who exhibited persistently elevated serum calcitonin levels (35–47 ng/L). The diagnostic assessment comprised thyroid autoantibody panels, high-resolution ultrasound, serial fine-needle aspiration cytology (FNAC) with calcitonin washout measurements, a calcium stimulation test, and genetic testing for RET proto-oncogene mutations. The patient then had a total thyroidectomy and removal of the central lymph nodes.

The preoperative workup showed that the levels of anti-thyroglobulin and anti-thyroid peroxidase antibodies were very high, and the TSH level was also high (8.1 mIU/L). An ultrasound revealed two iso- to hypoechoic nodules and several cervical lymph nodes that appeared suspicious. FNAC results differed among samples: some were Bethesda II–III, while others were non-diagnostic. One nodule had a calcitonin washout level of 92 ng/L. The calcium stimulation test yielded a robust positive response, with peak calcitonin levels surpassing 500 ng/L (579 ng/L at 2 minutes). The genetic test for RET mutations came back negative. Following total thyroidectomy, histopathology confirmed nodular hyperplasia without evidence of MTC and all resected lymph nodes showed only reactive changes. After surgery, serum calcitonin levels returned to normal.

This case demonstrates that a combination of moderately elevated basal calcitonin levels, a positive calcitonin washout from FNAC, and a strong response to calcium stimulation—exceeding recently

ÖZ

Bu olgu sunumu, nodüler tiroid hastalığı olan bir hastada biyokimyasal bulguların medüller tiroid karsinomunu (MTK) güçlü bir şekilde işaret etmesine karşın histopatolojik analizin sonuçta benign nodüler hiperplazi ve C hücre aktivasyonunu tanımladığı, persistan yüksek kalsitonin düzeyleriyle ilişkili tanısal zorlukları incelemektedir.

Persistan yüksek serum kalsitonin düzeyleri (35–47 ng/L) sergileyen hipotiroidili 35 yaşında bir erkek hastayı tanımlıyoruz. Tanısal değerlendirme, tiroid otoantikor panelleri, yüksek çözünürlüklü ultrasonografi, seri ince iğne aspirasyon sitolojisi (İİAS) ve yıkama sıvısında kalsitonin ölçümü, kalsiyum stimülasyon testi ve RET proto-onkogen mutasyonları için genetik testten oluşmaktaydı. Hastaya ardından total tiroidektomi ve santral lenf nodlarının çıkarılması uygulandı.

Preoperatif değerlendirme, anti-tiroglobulin ve anti-tiroid peroksidaz antikor düzeylerinin oldukça yüksek olduğunu ve TSH düzeyinin de yüksek (8,1 mIU/L) olduğunu gösterdi. Ultrasonografi, iki adet izo-hipoekoik nodül ve şüpheli görünen birkaç servikal lenf nodu ortaya koydu. İİAS sonuçları her örnekte farklılık gösterdi; bazıları Bethesda II ile III arasında değerlendirilirken bazıları tanısal olarak değerlendirilemedi. Bir nodülde yıkama kalsitonin düzeyi 92 ng/L idi. Kalsiyum stimülasyon testi güçlü bir pozitif yanıt verdi; pik kalsitonin düzeyleri 500 ng/L'yi aştı (2. dakikada 579 ng/L). RET mutasyonlarına yönelik genetik test negatif sonuçlandı. Total tiroidektomi sonrasında histopatoloji, MTK bulgusu olmaksızın nodüler hiperplaziyi doğruladı ve çıkarılan tüm lenf nodlarında yalnızca reaktif değişiklikler izlendi. Cerrahi sonrasında serum kalsitonin düzeyleri normale döndü.

Bu olgu, orta derecede yüksek bazal kalsitonin düzeyleri, İİAS elde edilen pozitif yıkama kalsitonin sonucu ve yakın tarihte önerilen cinsiyete özgü eşik değerlerini aşan güçlü bir kalsiyum stimülasyon yanıtının bir arada

Cite this article as: Bayram SM, Demirci H, Canlar Ş, Cinel M, Karaçalık C, Çakal E. Marked Hypercalcitoninemia without medullary thyroid carcinoma: a case report. Gazi Med J. 2026;37(3):446-449

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Received/Geliş Tarihi: 02.04.2026
Accepted/Kabul Tarihi: 22.06.2026
Publication Date/Yayınlanma Tarihi: 10.07.2026

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ABSTRACT

suggested sex-specific thresholds—does not conclusively indicate MTC. Nodular hyperplasia with functional C cell activation can closely resemble the biochemical profile of medullary carcinoma. Our results demonstrate the importance of integrating biochemical, cytological, and histopathological data to avoid overly aggressive surgery. Reporting these cases helps to improve diagnostic thresholds and shows that a careful, step-by-step approach is needed to evaluate hypercalcitoninemia, particularly in distinguishing between nodular hyperplasia and medullary carcinoma.

Keywords: Thyroid neoplasms, calcitonin, C-cell hyperplasia, Hashimoto's disease

ÖZ

bulunmasının MTK kesin olarak göstermediğini ortaya koymaktadır. Fonksiyonel C hücre aktivasyonu ile birlikte görülen nodüler hiperplazi, medüller karsinomun biyokimyasal profilini yakından taklit edebilir. Bulgularımız, aşırı agresif cerrahiden kaçınmak için biyokimyasal, sitolojik ve histopatolojik verilerin bütünleştirilmesinin ne denli önemli olduğunu göstermektedir. Bu tür olguların raporlanması, tanısal eşik değerlerin iyileştirilmesine katkı sağlamakta ve özellikle nodüler hiperplazi ile medüller karsinom arasında ayrım yapılmasında hiperkalsitoninemiyi değerlendirmek için dikkatli, adım adım ilerleyen bir yaklaşımın gerekliliğini vurgulamaktadır.

Anahtar Sözcükler: Tiroid neoplazileri, kalsitonin, C-hücre hiperplazisi, Hashimoto hastalığı

INTRODUCTION

Calcitonin is a peptide hormone made up of 32 amino acids that is released by the parafollicular C-cells in the thyroid gland (1). Calcitonin is a sensitive and specific biomarker for medullary thyroid carcinoma (MTC), and the number of C-cells in the blood directly reflects their number in the body (2,3). Elevated calcitonin levels are typically associated with malignancy, but nonmalignant such as C-cell hyperplasia (CCH), chronic thyroiditis, renal insufficiency, neuroendocrine tumors, and certain medications can also cause hypercalcitoninemia (4-6).

MTC is uncommon, making up only 2–3% of thyroid cancers in women and 4–5% in men (7). Its prevalence among patients with nodular thyroid disease has been reported to range from 0.3% to 1.4% (8,9). Some people have suggested that patients with thyroid nodules should have their serum calcitonin levels monitored regularly, but the cost-effectiveness of this strategy remains uncertain because MTC is rare and false-positive results can occur (9-12). In Europe, guidelines generally recommend that calcitonin levels be measured in patients with nodular thyroid disease. The American Thyroid Association, on the other hand, does not take a position (2,13). Assay interference, heterophilic antibodies, or natural factors like sex, age, and smoking (6,14-18) can all cause calcitonin levels to be falsely high. Furthermore, only 10–40% of individuals with both high basal calcitonin levels and thyroid nodules are eventually diagnosed with MTC (6,9). This gray area between normal and abnormal values makes it difficult to establish clear cutoff points. Basal calcitonin levels over 100 pg/mL are generally considered indicative of the need for surgery (2). However, levels below this threshold often require additional testing, such as immunocytochemistry, measurement of calcitonin in fine-needle aspiration washout fluid, or stimulation tests with pentagastrin or calcium (11,19-21).

CCH has been documented in conjunction with Hashimoto thyroiditis and multinodular goiter. Histologically, CCH is characterized by an elevated C cell density (>40 cells/cm²) or by the presence of multiple microscopic foci, each exceeding 50 C-cell per field. Hereditary CCH is thought to represent a precancerous stage of MTC, but there have also been reports of sporadic cases that did not progress to cancer (22-24).

Beyond the classical MTC framework, high calcitonin levels in nodular thyroid disease may result from benign C-cell activity, assay interference, or systemic factors such as medications and other comorbid conditions. If calcitonin levels return to normal after surgery and there is no histopathological evidence of MTC, the hormone excess likely originated from nodular thyroid tissue containing hyperplastic or functionally active C-cells. Such cases underscore the importance of combining biochemical markers with histopathological findings to avoid misclassification and unnecessarily aggressive management (25).

This case provides an opportunity to examine the broader context of the differential diagnosis of hypercalcitoninemia. It emphasizes the need for careful interpretation of calcitonin dynamics, strict adherence to assay methods, and a step-by-step diagnostic algorithm to avoid overtreatment of patients with nodular thyroid disease.

CASE PRESENTATION

A 35-year-old male patient was referred for testing because his serum calcitonin levels were consistently elevated. His medical history was otherwise unremarkable, with no family history of thyroid malignancy, chronic comorbidities, or alcohol or tobacco use. He was taking 50 mcg/day of levothyroxine for hypothyroidism.

Laboratory tests performed before surgery showed serum calcitonin levels ranging from 35 to 47 ng/L (normal range for men is less than 10 ng/L). The thyroid autoantibodies were positive. The anti-thyroglobulin (anti-TG) antibody was 596 IU/mL (reference: <115 IU/mL), and the anti-thyroid peroxidase (anti-TPO) antibody was 286 IU/mL (reference: <35 IU/mL). The thyroid-stimulating hormone level was elevated at 8.1 mIU/L (normal range: 0.4–4.0 mIU/L). Prolactin was 10 ng/mL (normal range: 4–15 ng/mL), which is within the normal range. The reference range for serum calcium is 8.5–10.5 mg/dL, and for gastrin is 0–100 pg/mL. The levels of catecholamine metabolites in the plasma were normal.

Thyroid ultrasound showed two iso-hypoechoic nodules: one in the right upper lobe, measuring 7 × 7 × 9.5 mm, and the other in the left lower lobe, measuring 5 × 6 × 7 mm. Some cervical lymph nodes were found in the central and lateral compartments. They ranged in size from 4 to 13 mm; some had a poorly defined echogenic hilum, which made them suspicious but not diagnostic for cancer.

Fine needle aspiration cytology (FNAC) was conducted on several occasions. The right upper nodule contained inflammatory infiltrates composed predominantly of lymphocytes and lacked thyrocytes in July 2024. There was no calcitonin washout. In September 2024, the same nodule was classified as benign follicular nodular disease

(Bethesda II), again without calcitonin washout. In November 2024, FNAC from the right upper nodule was non-diagnostic, but calcitonin washout was high at 92 ng/L. A second aspiration of the right upper lateral nodule did not yield useful information, and the calcitonin washout was less than 0.5 ng/L. FNAC of the left lower nodule showed a follicular lesion of unknown significance (Bethesda III) and a calcitonin washout of less than 0.5 ng/L.

Subsequently, provocative testing was performed. The omeprazole stimulation test was negative (Table 1). A calcium stimulation test showed a marked increase in serum calcitonin to levels exceeding 500 ng/L (Table 1). No evidence of the RET proto-oncogene by the genetic test.

Based on these results, a multidisciplinary tumor board suggested surgery. In December 2024, the patient had a total thyroidectomy and dissection of both central lymph nodes.

Histopathological analysis indicated nodular hyperplasia of the thyroid gland, with no signs of MTC. All examined lymph nodes exhibited reactive alterations without evidence of metastatic infiltration. After surgery, serum calcitonin levels returned to normal. This supports the idea that the high levels of calcitonin before surgery came from nodular thyroid tissue with hyperplastic or functionally active C-cells instead of medullary carcinoma.

DISCUSSION

In this case, a 35-year-old man had basal serum calcitonin levels that ranged from 35 to 50 ng/L, a fine-needle aspiration washout calcitonin level of 92 ng/L, and a calcium stimulation test that was markedly positive, with values of 579 ng/L at 2 minutes, 534 ng/L at 5 minutes, 524 ng/L at 7 minutes, and 468 ng/L at 10 minutes. Even though these biochemical results were present, histopathology after a total thyroidectomy showed only nodular hyperplasia and no MTC. After the surgery, calcitonin levels returned to normal. This result shows that nodular hyperplasia with C cell activation can mimic the biochemical profile of MTC without becoming malignant.

Calcitonin is a well-known biomarker for MTC, but it is not highly specific, especially when levels are only slightly to moderately elevated. False-positive results have been linked to autoimmune thyroiditis, multinodular goiter, differentiated thyroid carcinoma, renal insufficiency, and drugs like proton pump inhibitors. Both anti-TG and anti-TPO antibodies were markedly elevated in our patient, indicating autoimmune thyroiditis. This condition has also been linked to changes in calcitonin secretion. The 92 ng/L FNA washout calcitonin result supports the presence of active C-cells in the nodular tissue.

Table 1. Comparative table of stimulation tests applied to our patient.

Test type	Time point	Calcitonin (ng/L)	Gastrin (pg/mL)	Reference range (gastrin)
Omeprazole	Day 1	43.6	19.3	0–100 pg/mL
Omeprazole	Day 2	45.0	–	0–100 pg/mL
Omeprazole	Day 3	38.4	96.0	0–100 pg/mL
Omeprazole	Day 4	36.6	177.0	0–100 pg/mL
Calcium	Baseline	~45.0	–	N/A
Calcium	2 min	579.0	–	N/A
Calcium	5 min	534.0	–	N/A
Calcium	7 min	524.0	–	N/A
Calcium	10 min	468.0	–	N/A

The calcium stimulation test for this patient showed levels above 500 ng/L, which recent research suggests are highly suspicious for MTC. Sesti et al. (26) conducted a meta-analysis of individual-patient data and found different thresholds for calcium stimulation testing in men and women. They suggested that the cutoff values should be 562 pg/mL for men and 162 pg/mL for women. The pooled sensitivity for men was 0.79, specificity 0.89, and area under the curve 0.94, indicating that the test was highly accurate. The patient's peak value of 579 ng/L exceeded the male cutoff; however, histology showed no evidence of cancer. This shows that false positives can occur even when stimulated values exceed suggested thresholds. This difference highlights the importance of combining stimulation-test results with cytology, FNA-washout calcitonin, autoantibody status, and histopathology before deciding on aggressive surgery. Our case adds to this evidence by showing that nodular hyperplasia with C cell activation can cause values higher than the new male cutoff.

This case demonstrates several important points. Thresholds are not always accurate, and even sex-specific cutoffs from a meta-analysis may yield false positives. High levels of autoantibodies may indicate autoimmune thyroiditis, which is linked to C cell hyperplasia and a possible rise in calcitonin levels. If there are moderate basal elevations, you should obtain additional measurements, perform an FNA washout for calcitonin, and carefully consider the stimulation test results before surgery. Recording cases of non-MTC hypercalcitoninemia that normalize after surgery is useful for refining cutoff values and improving the specificity of clinical practice. Future studies examining procalcitonin, calcitonin, FNA washout calcitonin, and stimulation tests may help determine which hormone elevations are attributable to cancer and which are not.

This case demonstrates that a basal calcitonin level in the range of 45–50 ng/L, a positive fine-needle aspiration washout calcitonin level of 92 ng/L, and a calcium stimulation peak exceeding the recommended male cutoff of 562 pg/mL do not, in isolation, confirm the presence of MTC. Even though it was higher than what a recent meta-analysis suggested (26), histology showed nodular hyperplasia, and calcitonin levels returned to normal after surgery. To avoid unnecessarily aggressive treatments, doctors should interpret the results of stimulation tests in the broader clinical and pathological context. Reporting these cases contributes to refining diagnostic algorithms and underscores the need for prospective studies to validate sex-specific thresholds and to integrate additional markers in the evaluation of thyroid nodules.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.M.B., H.D., Ş.C., M.C., C.K., E.Ç., Concept: S.M.B., E.Ç., Design: S.M.B., H.D., Data Collection or Processing: S.M.B., Ş.C., M.C., C.K., Analysis or Interpretation: S.M.B., H.D., E.Ç., Literature Search: S.M.B., C.K., Writing: S.M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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