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PERSISTENT HYPERPROCALCITONINEMIA AS THE INITIAL DIAGNOSTIC CLUE TO SPORADIC MEDULLARY THYROID CARCINOMA

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ABSTRACT

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumour arising from parafollicular C cells, and serum calcitonin remains its most reliable biochemical marker. Procalcitonin (PCT), widely used in the evaluation of bacterial infections, is usually undetectable under non-infectious conditions. Persistent elevation of PCT in the absence of clinical or microbiological evidence of infection is uncommon and may represent an early clue to underlying endocrine malignancy.

We report the case of a 48-year-old woman who presented with markedly elevated PCT levels (>20 ng/ml) detected during routine laboratory testing despite being asymptomatic and having normal inflammatory markers. Extensive infectious work-up was negative, and antibiotic therapy did not reduce PCT levels. Further endocrine evaluation revealed a calcitonin level >2000 ng/l, elevated carcinoembryonic antigen, and a suspicious thyroid nodule on ultrasonography. Fine-needle aspiration with calcitonin washout confirmed the diagnosis of MTC. The patient underwent total thyroidectomy with central neck dissection, and histopathology demonstrated a 4.5 cm sporadic MTC without nodal metastasis. Postoperative PCT and calcitonin levels declined markedly, supporting their parallel behaviour in relation to disease activity.

This case highlights the clinical importance of considering MTC in patients with unexplained hyperprocalcitoninemia and supports the potential role of PCT as an adjunct biomarker in diagnostic evaluation and postoperative monitoring once infection has been excluded.

KEYWORDS

Procalcitonin, medullary thyroid carcinoma, calcitonin, neuroendocrine tumour, case report

LEARNING POINTS

- Persistent elevation of procalcitonin in the absence of infection should raise suspicion for medullary thyroid carcinoma and other neuroendocrine malignancies.
- Procalcitonin may serve as a useful adjunct biomarker alongside calcitonin in the diagnostic evaluation and postoperative follow-up of medullary thyroid carcinoma.
- Awareness of non-infectious causes of hyperprocalcitoninemia can prevent unnecessary antimicrobial therapy and reduce diagnostic delay in internal medicine practice.

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INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine malignancy arising from parafollicular C cells and represents approximately 3–5% of all thyroid cancers[1,2]. Despite its relatively low prevalence, MTC accounts for a considerable proportion of thyroid cancer–related mortality because of its heterogeneous biological behaviour and the limited effectiveness of systemic therapies in advanced disease[1-3]. Since MTC does not take up radioactive iodine, early diagnosis followed by complete surgical resection remains the cornerstone of successful management[2-5]. Serum calcitonin serves as a sensitive and specific biochemical marker for the diagnosis, staging, and postoperative surveillance of MTC, and markedly elevated levels are considered highly suggestive of the disease[6,7]. In contrast, procalcitonin (PCT), a 116–amino acid precursor of calcitonin, is typically undetectable in healthy individuals and is widely used as a biomarker for bacterial infections and sepsis[8,9]. During systemic infection, cytokine-driven extrathyroidal production of PCT increases substantially, resulting in high serum levels.

Persistent hyperprocalcitoninemia in the absence of infection is uncommon and should prompt evaluation for alternative aetiologies, including neuroendocrine tumours such as MTC[6,10]. Emerging evidence suggests that PCT may correlate with tumour burden and be a biomarker for the diagnosis of MTC comparable to calcitonin in selected clinical contexts[6,8,11]. Furthermore, an elevated PCT-to-calcitonin ratio has been associated with more aggressive disease characteristics[12]. Nevertheless, awareness of this association remains limited, and patients with unexplained PCT elevation are frequently subjected to unnecessary infectious disease evaluations and antimicrobial therapy, potentially delaying the diagnosis of MTC[6,12].

In this report, we present a case of sporadic MTC identified during the evaluation of persistent, unexplained hyperprocalcitoninemia in an asymptomatic female patient. This case highlights the clinical importance of considering MTC in patients with elevated PCT levels once infection has been excluded and underscores the potential role of PCT as an adjunct biomarker in both diagnostic assessment and postoperative monitoring.

CASE DESCRIPTION

A 48-year-old woman with no remarkable medical or family history was evaluated in the internal medicine clinic after a markedly elevated PCT level was detected during routine laboratory assessment. The PCT measurement had been performed to exclude a possible bacterial infection as part of the initial clinical evaluation, despite the absence of fever, weight loss, localized infectious symptoms, or recent hospitalization. Physical examination was unremarkable, and there were no clinical signs suggestive of infection or systemic inflammation. The patient denied respiratory or urinary symptoms, recent infections, and was not receiving antibiotics or immunosuppressive therapy.

Parameter	Observation
Nodule location	Right thyroid lobe
Size (mm)	45 × 30 × 34
Characteristics	Solid, hypoechoic, peripheral halo, irregular margins, microcalcifications
ACR-TIRADS category	4
Suspicious lymph nodes	None detected

Table 1. Imaging findings.
Abbreviations: ACR-TIRADS: American College of Radiology Thyroid Imaging Reporting and Data System.

Given the absence of clinical or laboratory evidence of infection, further evaluation was initiated. Neck ultrasonography demonstrated a 45 × 30 × 34 mm hypoechoic solid nodule with a peripheral halo, irregular margins, and microcalcifications located in the right thyroid lobe, classified as American College of Radiology Thyroid Imaging Reporting and Data System 4. No suspicious cervical lymphadenopathy was identified. Imaging characteristics are summarized in *Table 1*.

Initial laboratory assessment revealed a markedly elevated PCT level of 21.1 ng/ml (reference <0.05 ng/ml). Repeat measurements obtained at one- and two-week intervals demonstrated persistently elevated levels ranging from 19.8 to 22.3 ng/ml. Inflammatory markers were within normal limits, with a C-reactive protein level of 4.2 mg/l and a leukocyte count of 7.1 $\times 10^9$/l. Blood and urine cultures remained sterile. Empirical treatment with intravenous ceftriaxone followed by oral levofloxacin for 10 days failed to reduce PCT levels Given the extraordinarily high PCT levels, repeat analysis was performed, including evaluation in an independent laboratory, and serial dilution was applied to exclude assay saturation or analytical interference, confirming the accuracy of the measured values. Key laboratory findings at presentation are shown in *Table 2*.

Given the persistently elevated PCT levels in the absence of infection, further endocrine evaluation was pursued. Serum calcitonin was markedly increased (>2,000 ng/l), and carcinoembryonic antigen (CEA) levels were also elevated (180 ng/ml), raising suspicion for MTC.

Fine-needle aspiration biopsy of the thyroid nodule was performed, and cytological evaluation suggested a neuroendocrine neoplasm. Measurement of calcitonin in the needle washout fluid confirmed the diagnosis of MTC. Immunocytochemical staining was positive for calcitonin, chromogranin A, and CEA, and negative for thyroglobulin. Differential diagnostic conditions associated with concomitant elevations of calcitonin and PCT are summarized in *Table 3*.

The patient subsequently underwent total thyroidectomy with central compartment (level VI) neck dissection. A firm, well-circumscribed tumour was identified in the

right thyroid lobe, with no gross extrathyroidal extension. Histopathological examination revealed a 4.5 cm medullary thyroid carcinoma confined to the thyroid gland. All twelve dissected lymph nodes were negative for metastatic involvement, corresponding to stage pT3aN0M0 according to the American Joint Committee on Cancer 8th edition.

Postoperative recovery was uneventful. Calcitonin and PCT levels declined significantly within 4 weeks and approached near-normal values at the 3-month follow-up (calcitonin 18 ng/l; PCT 0.12 ng/ml). Rearranged during transfection (RET) proto-oncogene analysis was negative, confirming a sporadic form of MTC. At 6 months, the patient remained asymptomatic with no biochemical or radiological evidence of recurrence.

DISCUSSION

MTC is an uncommon neuroendocrine tumour arising from parafollicular C cells and accounts for approximately 3–5% of all thyroid malignancies[1,2]. Despite its rarity, MTC contributes disproportionately to thyroid cancer–related mortality because of its variable biological behaviour and the limited effectiveness of systemic therapies in advanced disease[1-3]. Early diagnosis is therefore crucial, as complete surgical resection remains the only potentially curative treatment.

Parameter	Result	Reference Range
PCT (ng/ml)	21.1	<0.05
CTN (ng/l)	>2000	<10
CEA (ng/ml)	180	<5
TSH (mIU/l)	1.92	0.4–4
Free T4 (ng/dl)	Normal	0.8–1.8
CRP (mg/l)	4.2	<5
WBC count (×10⁹/l)	7.1	4–10

Table 2. Key laboratory findings.
Abbreviations: PCT, procalcitonin; CTN, calcitonin; CEA, carcinoembryonic antigen; TSH, thyroid- stimulating hormone; T4, thyroxine; CRP, C-reactive protein; WBC: white blood cell.

Condition	Calcitonin	Procalcitonin
Bacterial sepsis	Variable	↑
Neuroendocrine tumours (MTC and others)	↑	↑
Chronic kidney disease	↑	↑
Autoimmune thyroiditis	↑	Normal
Proton pump inhibitors	↑	Normal
C-cell hyperplasia	↑	Normal

Table 3. Causes of hypercalcitoninemia and hyperprocalcitoninemia.
Abbreviations: MTC, medullary thyroid carcinoma.

Serum calcitonin is the most sensitive and specific biochemical marker for both the diagnosis and postoperative surveillance of MTC, with markedly elevated levels being highly predictive of the disease[1-3,13]. PCT, the prohormone of calcitonin, is widely used in clinical practice as a biomarker of bacterial infection and sepsis[8,9]. During systemic inflammation, extrathyroidal production of PCT leads to elevated circulating levels. In contrast, persistent PCT elevation in the absence of infection is unusual and should prompt consideration of alternative aetiologies, including neuroendocrine malignancies.

Previous studies have demonstrated that elevated PCT levels may reflect neuroendocrine tumour activity and can be observed in patients with MTC[6,10,14]. Several reports have shown a correlation between PCT levels and tumour burden, with diagnostic performance comparable to calcitonin in selected clinical settings[6,8,10,11]. Furthermore, an increased PCT-to-calcitonin ratio has been associated with more aggressive disease behaviour[12].

In the present case, markedly elevated PCT levels (>20 ng/ml) were identified incidentally in an asymptomatic patient. The absence of clinical signs of infection, normal inflammatory markers, negative microbiological studies, and lack of response to empirical antibiotic therapy made infectious causes unlikely. Subsequent endocrine evaluation revealed markedly elevated calcitonin and CEA levels, leading to the diagnosis of MTC. The parallel postoperative decline in both calcitonin and PCT levels further supports the concept that PCT may serve as an adjunct biomarker reflecting disease activity. This case supports the recommendation that further diagnostic evaluation should be considered primarily in patients with persistently elevated procalcitonin levels, rather than in cases of isolated or transient elevation.

This association has important clinical implications. Patients with unexplained hyperprocalcitoninemia frequently undergo repeated infectious workups or prolonged antimicrobial treatment before non-infectious causes are considered[6,12]. Increased awareness of the potential link between persistent PCT elevation and MTC may facilitate earlier diagnosis and help avoid unnecessary investigations or inappropriate therapies.

Several studies and meta-analyses have highlighted the potential role of PCT in the diagnosis and postoperative follow-up of MTC, noting its correlation with tumour burden and its decline after complete tumour resection[4-6,10,11,15,16]. Although calcitonin remains the gold standard biomarker, PCT offers certain analytical advantages, including widespread availability and reduced susceptibility to assay interference, such as heterophile antibodies[4,7,16].

In conclusion, this case emphasizes that persistent, unexplained elevation of PCT should not be attributed solely to infection. Consideration of neuroendocrine

malignancies such as MCT may prevent diagnostic delay and support timely, appropriate management in everyday internal medicine practice.

CONCLUSION

This case highlights the diagnostic relevance of persistent PCT elevation in the absence of infection and underscores the importance of considering MTC in the differential diagnosis of unexplained hyperprocalcitoninemia. Although calcitonin remains the primary biomarker for MTC, PCT may provide complementary clinical information, particularly when incidentally detected during routine or infection-related testing. The parallel postoperative fall in levels of both biomarkers in this patient supports the potential role of PCT in reflecting disease activity. Increased clinical awareness of this association may help prevent diagnostic delay and avoid unnecessary antimicrobial treatment in everyday internal medicine practice.

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