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CASE REPORT

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Calcitonin-secreting pancreatic neuroendocrine tumor in a patient with elevated thyroid fine-needle aspirate calcitonin washout: A case report and review of the literature

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Abstract

We report the unique case of a patient with previously proven non-functional PanNET and Graves' disease with thyroid nodules. The patient had elevated intranodular calcitonin, but no MTC or c-cell hyperplasia on thyroidectomy. They were found to have calcitonin secreting PanNET. This case presents a false-positive intranodular calcitonin.

KEYWORDS

calcitonin, calcitonin wash, medullary thyroid cancer, pancreatic neuroendocrine tumor

1 | INTRODUCTION

Calcitonin is a monomeric peptide derived from embryologic neurocrest cells. Elevations of calcitonin are classically associated with medullary thyroid carcinoma (MTC), though other causes of elevation have been described such as specific disease states, laboratory interferences, and medication interactions (Table 2). Diagnostic specificity for medullary thyroid carcinoma approaches 100% if calcitonin wash from a thyroid nodule FNA yields a calcitonin level greater than 100 pg/ml.[1,2] Here, we present a rare case in which a previously proven non-functional pancreatic neuroendocrine tumor (PanNET) developed into a calcitonin secreting pancreatic neuroendocrine tumor and was the etiology of an elevated calcitonin wash from thyroid FNA. To the best of our knowledge, this is the first case report demonstrating an elevated calcitonin from thyroid FNA which did not represent MTC or C-cell hyperplasia.

2 | CASE PRESENTATION

A 63-year-old man with history of Graves' disease, Graves' ophthalmopathy requiring emergency decompression surgery, thyroid nodules, non-smoker with remote smoking history in early 20s and previously proven non-functional well-differentiated (PanNET) status post-distal pancreatectomy and splenectomy (Ki-67 >20%) 6 years prior presents for follow-up. Prior workup to include serum calcitonin <0.2 pg/ml (0–8.4 pg/ml) when checked at time of initial diagnosis and 3.6 pg/ml (0–8.4 pg/ml) at 1 year follow-up. Surveillance imaging demonstrated stable subcentimeter somatostatin receptor binding over 4 year period, with concern for worsening metastasis on imaging in the months prior to re-evaluation to our institution. He presented with complaints of new-onset flushing, heat intolerance, fatigue, and weight loss. Laboratory workup revealed elevated serum calcitonin of 163 pg/ml. Insulin, glucose, C-Peptide, gastrin, VIP, glucagon, somatostatin, ACTH, serotonin, PTHrP, chromogranin A, and 24hr urine cortisol were performed to assess for functional PanNET but all returned within normal limits. PTH, calcium, prolactin, 24 h urine 5HIAA, and plasma metanephrines were performed to assess for other endocrinopathies contributing to symptoms but returned within normal limits. Thyroid function tests were normal while on antithyroidal drugs. He had elevated thyroid-stimulating immunoglobulins of 5.08 IU/L (0–0.55 IU/L) but thyroperoxidase antibody and thyroglobulin antibody were within normal limits (0–34 IU/ml and 0–0.9 IU/ml, respectively). Thyroid ultrasound demonstrated a right lower pole complex solid/cystic isoechoic nodule with increased vascularity measuring 3.29 cm (Figure 1). This represented a >50% increase in volume compared with prior thyroid ultrasound.

Per American Thyroid Association guidelines, repeat FNA was performed due to >50% increase in thyroid nodule volume and calcitonin washout was included due to elevated serum calcitonin. FNA revealed a follicular lesion of undetermined significance with elevated calcitonin washout of 171 pg/ml. Given the patient's symptoms of fatigue, weight loss and flushing, elevated calcitonin on thyroid FNA, and his history of Graves' disease with ophthalmopathy requiring decompression surgery, the patient underwent total thyroidectomy due to concern of MTC and for definitive treatment of Graves' disease. Antithyroid drugs and potassium iodide were appropriately administered pre-operatively with normalized thyroid function tests. Plasma metanephrines were normal prior to surgery. Neuron-specific enolase was 4.3 ng/ml (0–12.5 ng/ml), and carcinoembryonic antigen was 2.8 ng/ml (0.2–4.7 ng/ml). The patient was also referred to genetics for evaluation of multiple endocrine neoplasia type 2 (MEN2).

Surprisingly, histopathologic examination from the total thyroidectomy specimen demonstrated benign thyroid tissue without evidence of MTC or C-cell hyperplasia. Due to the patient's worsening symptoms of flushing, decreased PO intake, weight loss, and fatigue following surgery, repeat serum calcitonin was performed and returned elevated at 241 pg/ml. With MTC ruled out as the source of hypercalcitoninemia, a functional PanNET was considered. MRI abdomen revealed multiple discrete intrahepatic lesions with avid arterial enhancement that corresponded with 68-GA DOTATATE avidity. The patient underwent biopsy of the liver lesions which revealed well-differentiated neuroendocrine tumor (WHO Grade 2) and had immunoreactivity to calcitonin (Figure 2).

The patient was subsequently started on somatostatin analog therapy (octreotide) for well-differentiated,

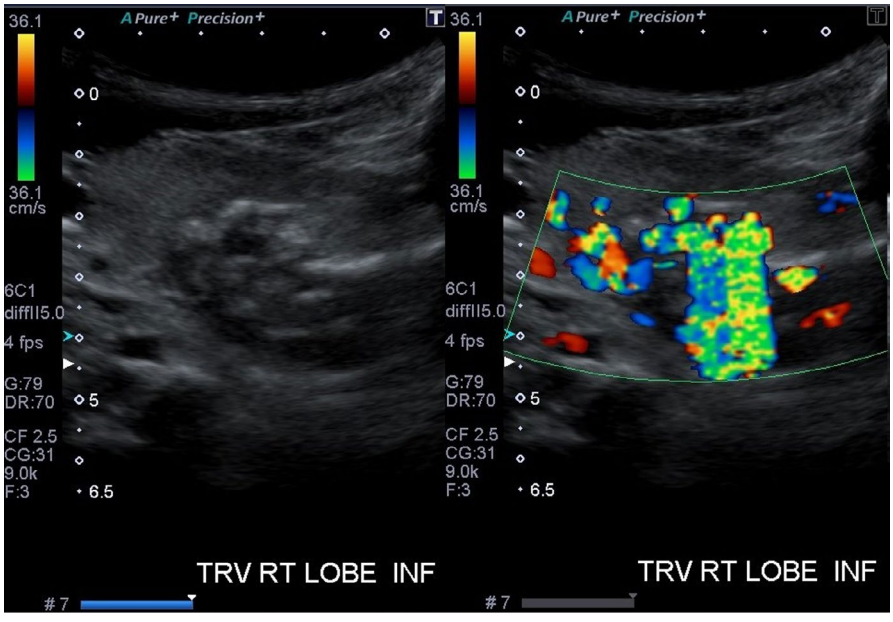

FIGURE 1 Thyroid ultrasound showing a 3.29 cm complex cystic/solid isoechoic thyroid nodule in the right lower pole. The right pane demonstrates the increased vascularity on color flow

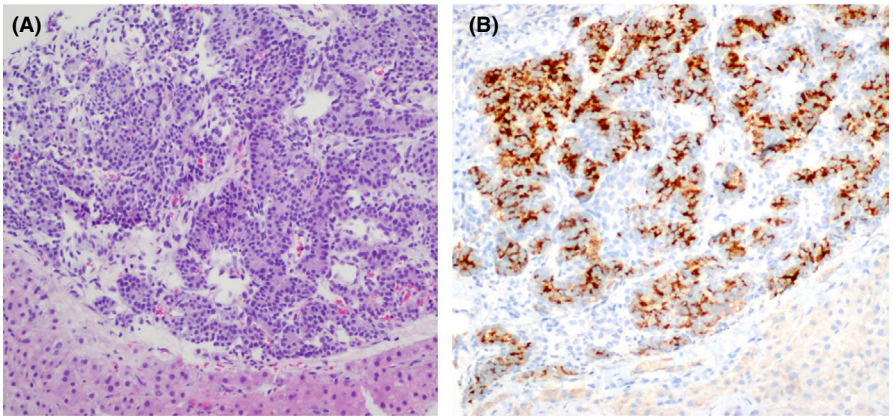

FIGURE 2 Liver biopsy demonstrating a well-differentiated pancreatic neuroendocrine tumor (A) with immunoreactivity to calcitonin. (B) Normal liver at the bottom displays no reactivity. The tumor was also reactive to synaptophysin and CD56, but unreactive to cytokeratins and TTF-1 (not shown)

metastatic PanNET as surgical resection was deemed to be ineffective given metastatic disease. Thyroid hormone replacement therapy was initiated immediately postoperatively and required frequent titration within the first 6 months of octreotide therapy. Calcitonin reduced to 123 pg/ml after 2 cycles of octreotide therapy (Table 1). The patient's symptoms of fatigue, weight loss, and flushing have gradually improved. MRI abdomen revealed stable hepatic masses after 6 months of octreotide therapy.

3 | DISCUSSION

Calcitonin is a 32-amino acid monomeric peptide derived from cleavage and post-translational processing of procalcitonin. Calcitonin is the main peptide product of thyroid C cells, but alternative expression of the gene is in neural tissue.[3] In the setting of a multinodular goiter, calcitonin is often used in the evaluation for underlying MTC. The American Thyroid Association Clinical Practice Guidelines for the management of MTC in 2015 do not recommend for or against routine measurement of serum calcitonin in patients with thyroid nodules given lack of prospective randomized trials, but should be obtained if there is a concern for MTC or MEN syndrome. Elevated levels should prompt further investigation.

One limitation to using serum calcitonin in evaluating for MTC is its lack of specificity since numerous factors can affect calcitonin levels (Table 2).[4–9] One of these factors, autoimmune thyroid disease, has been postulated to be associated with elevated calcitonin readings, but this is considered controversial and recent reviews

TABLE 1 PanNET treatment course and response to therapy with biochemical markers and imaging

Laboratory/Imaging (Reference range)	September 2015 (Post-pancreatectomy)	June 2020 (Initial elevated calcitonin)	August 2020 (Post-Total Thyroidectomy)	January 2021 (2 cycles octreotide)
Calcitonin (serum) (0–8.4 pg/ml)	3.6	163	246	123
Procalcitonin (0–0.25 ng/ml)		-	0.37	0.23
Chromagranin A (0–101.8 ng/ml)	3	40	-	37.4
Carcinoembryonic Ag (0.2–4.7 ng/ml)		3.1	2.7	-
Neuron-Specific enolase (0–12.5 ng/ml)		4.3		
Imaging results	MRI abdomen: Negative (post-surgical changes)	US: RLP 3.29cm enlarging thyroid nodule	MRI abdomen and DODATATE scan: multiple discrete intrahepatic lesions with avid arterial enhancement that corresponded with 68-GA DOTATATE avidity	MRI: Stable hepatic lesions

Conditions	Laboratory	Medications
Chronic renal disease	Heterophile antibodies	Proton pump inhibitors
Smoking status	Rheumatoid factor	H2 blockers
Obesity		Vitamin C
Hyperparathyroidism		Glucocorticoids
Autoimmune thyroiditis		Beta-blockers
Papillary thyroid cancer		
Prostate cancer		
Lung cancer (small cell and large Cell)		
Neuroendocrine tumors (enteric and pulmonary)		
Sepsis		

TABLE 2 Factors that may alter serum calcitonin levels

do not demonstrate an association between autoimmune thyroid disease and baseline calcitonin elevations.[10–14]

When MTC is considered as a possible diagnosis (and should always be investigated in the setting of elevated serum calcitonin), determining intra-thyroidal calcitonin (FNA-calcitonin) level has been found to be a reliable test. In one review from Japan of 201 nodules, 107 were MTC and had FNA-calcitonin levels ranging from 14 pg/ml to 6,600,000 pg/ml. 96.3% of these had a calcitonin >100 pg/ml. In the non-MTC nodules, FNA-calcitonin ranged from <10 to 1800 pg/ml, but 97.9% were less than 100 pg/ml, with the remaining 2 nodules demonstrating C-cell hyperplasia. This study found a 100 pg/ml cutoff for FNA-calcitonin to have 96.3% sensitivity and 97.9% specificity for MTC.[2] A smaller study of 38 MTC nodules from 36 patients found that an FNA-calcitonin value of 39.6 pg/ml had a 100% sensitivity and specificity for MTC.[1]

Our patient had an elevated FNA-calcitonin above the previously reported thresholds, yet his thyroid pathology was ultimately benign. We suspect that his elevated FNA-calcitonin was due to a markedly vascular thyroid, which is not atypical for a patient with Graves' disease (Figure 1).

Ultimately, the patient's elevated calcitonin was secondary to a pancreatic neuroendocrine tumor (PanNET). PanNETs are themselves a rare entity, with an annual incidence of 1:100,000 population. These tumors are nonfunctional in 60%–90% of reported cases, as this patient's was initially shown to be.[15,16] The most common functional PanNETs secret insulin, glucagon, and vasoactive intestinal peptide. Calcitonin secreting PanNET is exceedingly rare with an incidence of <0.01/million population/year.[17]

Treatment of PanNET can be surgical and/or medical. Surgical resection is the mainstay of treatment, and the only treatment that offers cure if diagnosed before metastasis. However, 65%–95% of patients are initially diagnosed with metastases which pertains a 13%–54% 3–5-year survival compared to 75%–99% for those diagnosed with local disease.[18] The National Comprehensive Cancer Network NET guidelines recommend somatostatin analogue therapy with octreotide or lanreotide as the first-line medical therapy. This recommendation is based off the PROMID study, a phase III trial of 85 patients showing median times to tumor progression of 14.3 months in the octreotide group compared to 6 months in the placebo group.[19] Similarly, the CLARINET study randomized 204 patients with pancreatic or intestinal NET to lanreotide or placebo group and found the lanreotide group had an improved 2-year progression-free survival.

4 | CONCLUSION

An elevated serum calcitonin should prompt further investigation for MTC. In a patient with a known neuroendocrine tumor and nodular thyroid disease, FNA-calcitonin may assist in localizing the calcitonin elevation to the thyroid. However, rarely an elevated FNA-calcitonin is not specific for MTC or C-cell hyperplasia, especially in the setting of increased thyroid vascularity. Clinicians should be aware of this possibility and considered in patient with thyroid gland hypervascularity (such as Graves' disease).

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None.

CONFLICTS OF INTEREST

The authors have no conflicting or commercial interests to report.

AUTHOR CONTRIBUTIONS

Darryl Mason coauthored the draft. Dr. Robert Leimbach coauthored the draft. Dr. Robert Kitz provided pathology images and review. Dr. Robert Vietor and Dr. Nicole Vietor provided critical review.

ETHICAL APPROVAL

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

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

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