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(CASE REPORT)

# Encapsulated Medullary Thyroid Carcinoma with Adenoma-Like Features: Diagnostic and Therapeutic Challenges, Case Report and Literature Review

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## Abstract

Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine thyroid malignancy arising from parafollicular C cells. It differs from differentiated thyroid carcinoma in its biochemical behavior, genetic associations, and surgical management. Encapsulated MTC is rare and may appear radiologically and grossly deceptively benign, creating diagnostic uncertainty when morphologic findings conflict with serum biomarkers.

We report a 47-year-old female with a slowly enlarging, well-circumscribed right thyroid nodule, no cervical lymphadenopathy, and markedly elevated serum calcitonin. Fine-needle aspiration (FNA) showed atypical spindle and polygonal cells with focal calcitonin and synaptophysin positivity, raising suspicion for MTC but precluding confident classification due to adenoma-like follicular architecture. A multidisciplinary review favored definitive surgery because the biochemical and profile outweighed the reassuring imaging findings. Total thyroidectomy with central neck dissection revealed a 3.1 cm well-encapsulated MTC with adenoma-like features, no capsular or vascular invasion, negative central nodes, and a somatic RET mutation. Postoperative calcitonin and CEA declined substantially.

This case emphasizes that encapsulation and follicular-patterned architecture should not exclude MTC when calcitonin is elevated. It also supports the need for integrated biochemical, cytologic, IHC, molecular, and multidisciplinary assessment in diagnostically discordant thyroid nodules.

**Keywords:** Medullary thyroid carcinoma; Adenoma-like features; Fine-needle aspiration; Immunohistochemical; Multiple endocrine neoplasia; RET mutation

## 1. Introduction

MTC is a rare thyroid malignancy, biologically distinct from follicular cell-derived thyroid tumors because it arises from calcitonin-producing parafollicular C cells. [1] Most cases are sporadic, although hereditary diseases associated with germline RET mutations and multiple endocrine neoplasia type 2 (MEN2A/2B) remain clinically important; therefore, biochemical evaluation and genetic assessment often have direct diagnostic and therapeutic implications. [1,2] Unlike papillary or follicular thyroid carcinoma, MTC is not primarily managed with radioiodine, and complete initial surgery remains the principal curative treatment for localized disease. [1,3]

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Preoperative recognition may be difficult because sporadic MTC is often presented as a solitary thyroid nodule, and FNA can be indeterminate, particularly when tumors show unusual spindle-cell, follicular, papillary, oncocytic, or hyalinizing-trabecular patterns. [4] Serum calcitonin and carcinoembryonic antigen (CEA) are therefore central diagnostic and surveillance markers, and RET testing further refines hereditary risk and, in advanced disease, therapeutic options. [1] Encapsulated MTC is a rare pattern in which a well-defined capsule may suggest a benign or low-risk neoplasm despite malignant C-cell differentiation. [5] This case deserved reporting because it illustrated a clinically important diagnostic conflict: a radiologically reassuring, encapsulated thyroid nodule with adenoma-like architecture, but a biochemical and IHC profile strongly suggestive of MTC.

## 2. Case Presentation

### 2.1. Clinical Presentation and Initial Investigations

A 47-year-old female presented to her primary care physician with a several-month history of a slowly enlarging anterior neck mass. She denied dysphagia, dysphonia, or compressive symptoms and reported no personal or family history of thyroid disease, MEN, or pheochromocytoma. She had no prior neck irradiation. On physical examination, a firm, non-tender, approximately 3 cm solitary nodule was palpable in the right thyroid lobe, without appreciable cervical lymphadenopathy. The remainder of the examination was unremarkable.

Initial laboratory investigations revealed normal thyroid-stimulating hormone and free thyroxine levels. Serum calcitonin was notably elevated at 410 pg/mL, and CEA was mildly elevated at 8.2 ng/mL. Serum calcium and parathyroid hormone levels were within normal limits. Genetic counseling was initiated, given the calcitonin elevation, and testing for RET proto-oncogene mutations was sent. Urinary catecholamines and plasma metanephrines were obtained to exclude pheochromocytoma before any planned intervention, and both returned within normal limits.

### 2.2. Radiographic Findings and Differential Diagnosis

Neck ultrasound demonstrated a well-defined, hypoechoic, 3.1 cm nodule in the right thyroid lobe with a complete sonographic halo suggesting encapsulation, without internal vascularity disruption or calcifications, and no sonographically suspicious cervical lymph nodes. CT of the neck and chest with contrast confirmed a well-encapsulated, non-invasive-appearing right thyroid mass without extracapsular extension, tracheal deviation, or mediastinal involvement. No pathologically enlarged lymph nodes were identified in the central or lateral compartments. The radiologic impression, somewhat reassuringly, suggested a benign or low-risk thyroid neoplasm. However, the markedly elevated calcitonin created diagnostic dissonance, keeping the clinical suspicion for MTC firmly considered.

Ultrasound-guided FNA with cell block preparation was performed. Cytology revealed clusters of loosely cohesive polygonal and spindle-shaped cells with granular cytoplasm and eccentrically placed nuclei, with occasional binucleated forms. IHC analysis of the cell block showed focal positivity for calcitonin and synaptophysin, with negative thyroglobulin staining, a pattern suggestive of but not conclusively diagnostic for MTC. It was noted that morphology was atypical and that a definitive cytologic diagnosis could not be rendered with confidence, given the partially follicular architecture seen in many cell clusters, raising the question of a neuroendocrine-differentiated follicular neoplasm versus MTC.

### 2.3. Multidisciplinary Tumor Board Discussion

Because the diagnosis remained uncertain, the case was reviewed by the multidisciplinary head and neck tumor board, including specialists in endocrinology, endocrine surgery, pathology, radiology, and oncology. The team considered three main possibilities: follicular adenoma with focal neuroendocrine differentiation, well-encapsulated MTC, and MTC with adenoma-like architectural features. The markedly elevated serum calcitonin level was the strongest objective finding. In addition, focal but definite positivity for calcitonin and synaptophysin on the cell block, along with absent thyroglobulin expression, supported a diagnosis of encapsulated MTC.

The board therefore recommended total thyroidectomy with central neck dissection as the definitive diagnostic and therapeutic approach, with the need for lateral compartment dissection to be determined intraoperatively.

### 2.4. Management and Final Diagnosis

The patient underwent total thyroidectomy with central neck dissection. Intraoperatively, the right lobe mass was found to be encapsulated and grossly non-invasive. No macroscopically suspicious central compartment nodes were

identified, although complete nodal clearance of level VI was achieved. Gross pathology revealed a 3.1 cm well-encapsulated, tan-pink nodule with a fibrous capsule and no gross capsular breach.

On microscopic examination, the challenge immediately became apparent. Greater than 70% of the tumor demonstrated classic MTC histology, with nests and trabeculae of polygonal cells in an amyloid-rich stroma (Figure 1 A, B, C, D, E, F), strongly and diffusely positive for calcitonin, chromogranin, synaptophysin, and CEA, with negative thyroglobulin (Staining only the follicular cells) (Figure 2 A, B, C). The remaining minority component showed a microfollicular and normal follicular architecture reminiscent of a follicular adenoma, with cells focally expressing thyroglobulin, creating a genuinely mixed histologic picture. After thorough sampling and multistep sectioning, no capsular or vascular invasion was identified. Central compartment lymph nodes were all free of metastatic disease. The final pathologic diagnosis was rendered as Encapsulated medullary thyroid carcinoma with adenoma-like features, pT2 N0, with the dominant MTC component comprising over 70% of tumor volume. RET mutational analysis subsequently returned positive for a somatic RET mutation, supporting the diagnosis and providing prognostic clarity.

### 2.5. Outcome and Follow-Up

Postoperatively, the patient recovered without complication. Calcium and parathyroid hormone levels were monitored closely, with transient hypocalcemia managed conservatively. Serum calcitonin measured six weeks postoperatively had fallen to 12 pg/mL, and CEA normalized, both encouraging indicators of biochemical near-completeness of resection.

The patient was enrolled in structured long-term surveillance, with serum calcitonin and CEA measurements every 6 months for the first 2 years and annual neck ultrasound. Should calcitonin levels plateau above the normal range or demonstrate a subsequent rise, cross-sectional imaging of the neck, chest, abdomen, and pelvis, and potentially axial skeletal imaging, should be pursued systematically to identify locoregional recurrence or distant metastasis.

This case serves as a compelling reminder that an encapsulated, radiologically reassuring thyroid mass, when accompanied by markedly elevated calcitonin, demands an unwavering index of suspicion for MTC, regardless of its deceptively benign architectural presentation.

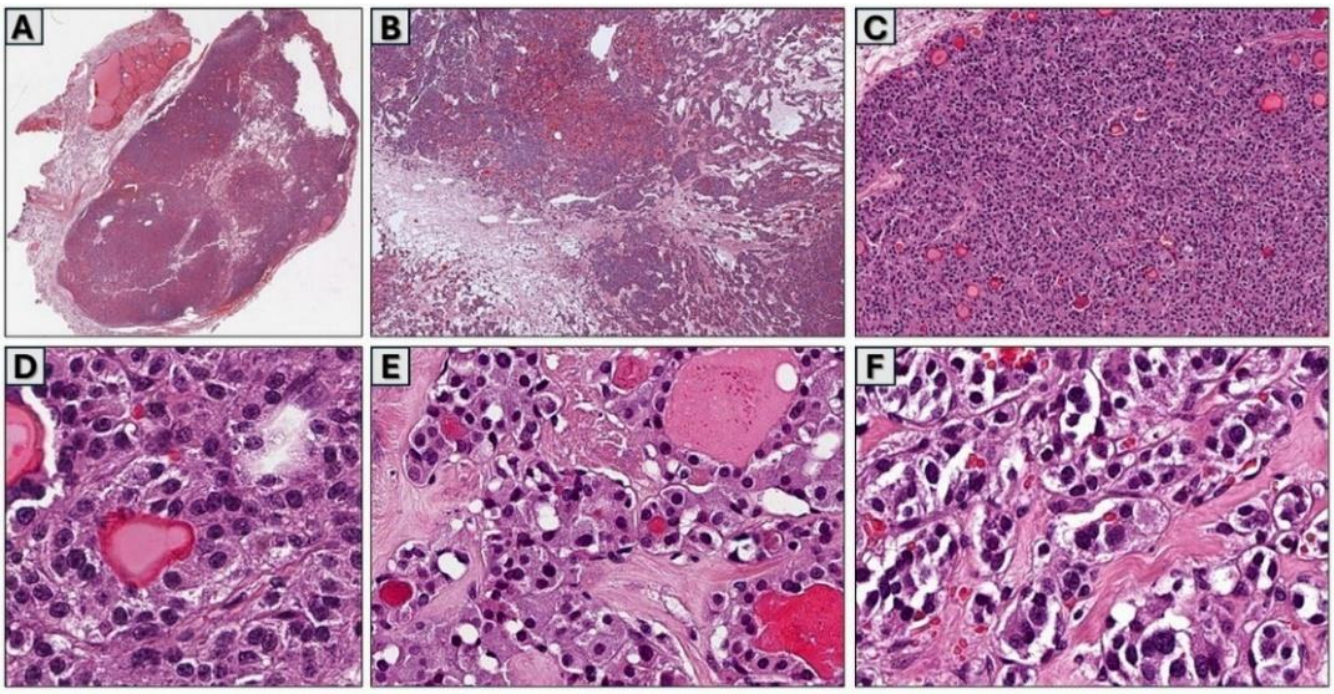


**Figure 1** Microscopic findings of the excised encapsulated medullary thyroid carcinoma

1A: Full low-power view showing a 3.1 cm well-encapsulated thyroid nodule (H&E stain X10).; 1B: Low power view showing complex microarchitectural and solid patterns with desmoplastic stroma (H&E stain X20); 1C: Intermediate power view showing solid component of the tumor (H&E stain X40).; 1D: High power view showing groups of follicular cells containing large eosinophilic cytoplasm (H&E stain X60); 1E: High power view showing cords, nest, and follicles in the background of desmoplastic stroma with amyloid deposits (H&E stain X60); 1F: High power view showing focal areas with pseudopapillary architecture (H&E stain X60)

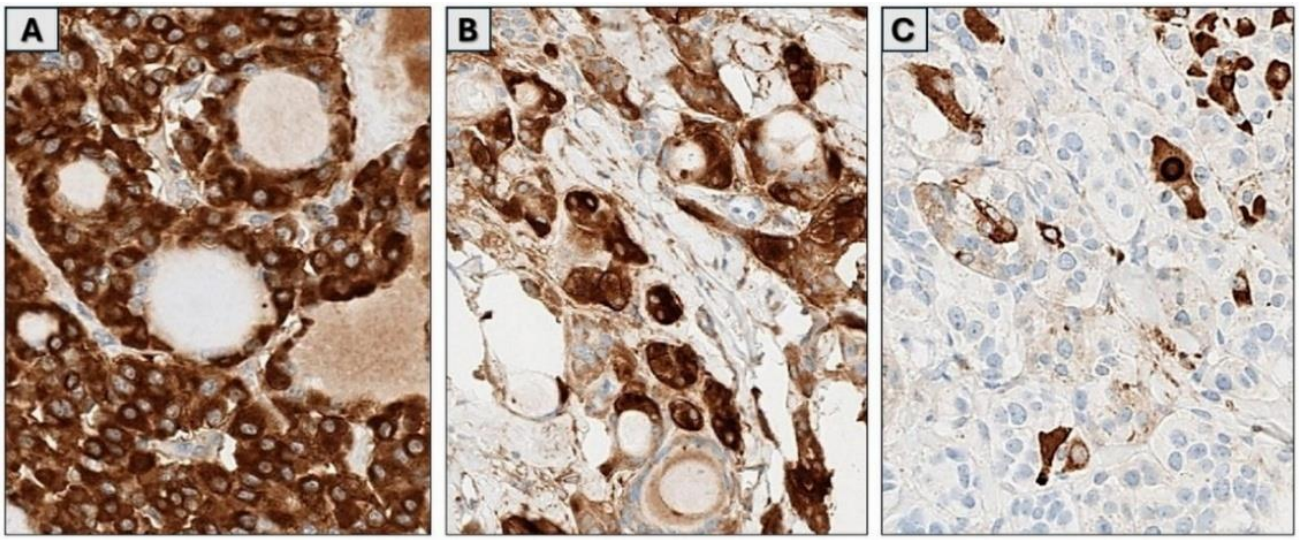


**Figure 2** Immunohistochemistry (IHC) studies on medullary thyroid carcinoma (MTC)

2A: Tumor cells positive for chromogranin; 2B Tumor cells positive for CEA; 2C: Tumor cells negative for thyroglobulin (Staining only residual follicular non-tumorous cells)

## 3. Discussion

### 3.1. Background (History, epidemiology, risk factors, and WHO classification)

Based on the most recent edition of the World Health Organization (WHO) classification of thyroid tumors, MTC is a rare malignant neuroendocrine tumor that arises from the parafollicular calcitonin-producing C cells of the thyroid. [6] It was first described by Hazard, Hawk, and Crile in 1959 as an independent pathological entity. [7] Among thyroid cancers, it is relatively uncommon, making up about 5-10% of all thyroid cancers, with papillary and follicular subtypes making up the majority (~90%). [8,9] Most of MTC cases occur sporadically (75-80%) and are usually isolated to one thyroid lobe. However, the disease can also be inherited as part of the MEN2A/B syndromes or familial FMTC. These syndromes are linked to missense, gain-of-function mutations of the RET (Rearranged during Transfection) proto-oncogene. [10]

The main risk factor for developing MTC sporadically is similar to those of other thyroid cancers, namely, radiation exposure (especially in children). It is three times more likely to occur in females than males and usually affects females in their 40s and 50s, and males in their 60s and 70s. [9] Mixed subtypes of MTC, although rare, may occur, namely mixed medullary-follicular and mixed medullary-papillary. Encapsulated MTC is also exceedingly rare, but the presence of a capsule in MTC has prompted discussion of its effects on prognosis. [5,6,11]

### 3.2. Pathogenesis, Pathophysiology

MTC is a neuroendocrine tumor that arises from parafollicular C cells, which are derived from neural crest cells. This tumor secretes calcitonin, which regulates calcium homeostasis, and its levels can be used to diagnose and monitor prognosis [12] The majority of MTCs are sporadic; however, some are associated with hereditary syndromes, such as MEN2A/2B. The underlying pathogenesis of MTCs associated with a hereditary syndrome is a gain-of-function mutation in the RET gene. The RET gene encodes a receptor tyrosine kinase. A mutation in this gene leads to activation of the tyrosine kinase, which then activates downstream signaling cascades such as MAPK and PI3K/AKT, thereby promoting tumor growth. [13,14] The sporadic form of MTC arises from somatic mutations in the RET and/or RAS genes. Targeting these genes could be a potential option for treating MTCs. This tumor also secretes CEA, and in a minority of cases, it secretes ACTH. [15]

The clinical features of this tumor are due to its hormonal activity and local growth. As this tumor grows, it can compress the adjacent structures, such as the trachea and esophagus, and cause dysphagia and hoarseness. MTCs can also spread to distal sites, such as the bone, lung, and liver. Excessive calcitonin secretion can lead to diarrhea and flushing. The other hormonal-related effect is due to ectopic ACTH secretion, which can lead to Cushing's syndrome [15] The amyloid deposition in the dense stroma is derived from calcitonin peptide. [16]

### 3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, lab, diagnosis, management, and outcome)

The present case shared several features with reported encapsulated MTCs. In the series and literature review by Contarino et al., 7 of 44 MTCs were encapsulated, none had nodal metastases, and all achieved clinical remission after surgery; across previously published cases, biochemical remission was reported in nearly all evaluable encapsulated tumors. [5] Similarly, our patient had a well-encapsulated 3.1 cm tumor, no extrathyroidal extension, no vascular or capsular invasion, negative central lymph nodes, and a marked postoperative decline in calcitonin and normalization of CEA. These findings aligned with the emerging observation that a complete capsule may correlate with lower metastatic potential, although available evidence remains limited and should not yet replace established surgical guidelines. [5,16]

The case also differed from many conventional MTCs, which are typically solid, firm, and non-encapsulated, and may show early lymphatic spread. [4] Its adenoma-like follicular component created a diagnostic pitfall similar to the hyalinizing trabecular adenoma-like MTC described by Santosh et al., in which spindle and ovoid cells and neuroendocrine chromatin were essential clues. [4] Conversely, true hyalinizing trabecular tumors and follicular adenomas are follicular-derived lesions that usually express thyroglobulin and lack calcitonin, chromogranin, and CEA staining, helping separate them from MTC. [17] In our case, the dominant diffuse positivity for calcitonin, chromogranin, synaptophysin, and CEA, thyroglobulin negativity in the MTC component, amyloid-rich stroma, and a somatic RET mutation favored encapsulated MTC rather than a benign follicular neoplasm with incidental neuroendocrine change.

## 4. What Have We Learned from This Case?

This case highlights the importance of maintaining a high index of suspicion for MTC when objective biochemical findings conflict with reassuring imaging and cytology, creating significant “diagnostic dissonance.”

The case was diagnosed as encapsulated MTC with adenoma-like features and not MMFC because it was proven to be a clonal tumor arising strictly from parafollicular C-cells. The tumor cells expressed neuroendocrine markers and were negative for thyroglobulin. The entrapment of benign, non-neoplastic thyroid follicles at the periphery of an expanding medullary tumor, or the formation of pseudofollicles by the malignant C-cells themselves, is a well-documented morphological pitfall. A tumor displaying such a massive percentage of C-cell malignancy 70% in our case) is treated according to MTC clinical protocols (e.g., assessing RET proto-oncogene mutation and tracking serum calcitonin). [11]

The most important lesson from this study is that markedly elevated serum calcitonin levels must be prioritized as a critical indicator of MTC, even when ultrasound and CT findings suggest a benign, well-encapsulated lesion. This case also underscores the diagnostic complexity of MTC, as adenoma-like or follicular architectural patterns on cytology and histology can closely mimic follicular neoplasms, leading to misleading interpretations. Consequently, reliance on a single diagnostic modality, such as FNA, is insufficient, underscoring the need for a multidisciplinary approach integrating imaging, laboratory evaluation, pathology, and molecular testing. Before definitive surgical intervention, pheochromocytoma and MEN syndromes must be excluded.

The successful management of this patient with total thyroidectomy and central neck dissection demonstrates the importance of acting on strong biochemical evidence despite atypical morphology. Furthermore, identification of a somatic RET mutation and normalization of postoperative calcitonin levels underscore the value of molecular testing and rigorous surveillance, including serial serum calcitonin and CEA monitoring with annual neck ultrasound.

In future practice, biochemical markers should remain a decisive component of evaluation, as MTC may present atypically despite otherwise reassuring findings.

**Abbreviations**: Medullary thyroid carcinoma (MTC); Fine-needle aspiration (FNA); immunohistochemical (IHC); Multiple endocrine neoplasia (MEN)

## 5. Conclusion

This case was presented because it highlighted a practical diagnostic and therapeutic challenge: a thyroid nodule may appear encapsulated, orderly, and adenoma-like, yet still represent medullary thyroid carcinoma when biochemical and IHC evidence point toward C-cell malignancy. The case added to the limited literature on encapsulated MTC by

documenting a pT2N0 tumor with adenoma-like features, the absence of capsular and vascular invasion, a somatic RET mutation, and a favorable early biochemical response after definitive surgery.

The value for the medical community lies in the lesson that diagnostic confidence in such cases should not rest solely on architectural factors. Markedly elevated calcitonin should prompt careful cytologic review, neuroendocrine immunostaining, RET evaluation, exclusion of MEN2-associated conditions when appropriate, and multidisciplinary planning. Recognizing this pattern may prevent under-treatment of an apparently benign thyroid nodule while also enriching the discussion about whether encapsulation identifies a biologically favorable subgroup of MTC.

## Compliance with ethical standards

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All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

### *Statement of ethical approval*

The present research work does not contain any studies performed on animals/humans' subjects by any of the authors. This study was conducted as a retrospective review of archival pathology material collected during routine clinical care. All data were fully de-identified prior to analysis.

### *Data access statement*

All relevant data are included in the paper.

### *Author contributions*

All authors contributed equally to producing this manuscript.

### *Statement of informed consent*

Informed consent for the publication of this case was obtained from the patient.

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