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High-Grade Medullary Thyroid Carcinoma With Tuberculous Cervical Lymphadenitis: A Diagnostic Challenge During Postoperative Surveillance

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Abstract

Medullary thyroid carcinoma (MTC) and tuberculous cervical lymphadenitis may coexist and create substantial diagnostic uncertainty during postoperative surveillance. We report a 61-year-old woman with a history of cervical tuberculosis who underwent total thyroidectomy with bilateral cervical lymph node dissection for a nodular goiter. Histopathological examination unexpectedly revealed multifocal high-grade MTC with regional lymph node metastases, reported as pT4aN1a. Tumor cells showed diffuse and strong calcitonin immunoreactivity; the Ki-67 proliferation index was 35%, and no tumor necrosis was identified. Cervical lymph node tissue additionally showed epithelioid granulomatous inflammation with multinucleated giant cells and caseous necrosis; tuberculosis was supported by a positive Xpert MTB/RIF (GeneXpert) assay. Postoperative tumor markers were initially elevated but showed marked improvement during follow-up, with carcinoembryonic antigen returning to the reference range while calcitonin remained above normal. Serial imaging demonstrated an indeterminate left thyroid bed lesion and an initially suspicious sternal scintigraphic abnormality that regressed and was not corroborated by computed tomography or fluorodeoxyglucose positron emission tomography/computed tomography. Fine-needle aspiration cytology and calcitonin measurement in needle washout from the cervical lesion were inconclusive. Germline RET analysis performed on peripheral blood genomic DNA identified a heterozygous pathogenic c.1858T>C (p.Cys620Arg) variant. This case emphasizes the need to integrate histopathology, microbiology, tumor marker kinetics, molecular genetics, and longitudinal imaging before attributing postoperative abnormalities to persistent or metastatic MTC.

Categories: Pathology, Oncology, Endocrinology/Diabetes/Metabolism
Keywords: calcitonin, cervical lymphadenitis, medullary thyroid carcinoma, ret, thyroid cancer, tuberculosis

Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine malignancy derived from thyroid parafollicular C cells. Serum calcitonin and carcinoembryonic antigen (CEA) are the principal biochemical markers used after surgery, and longitudinal marker kinetics are integrated with structural imaging to assess persistent or recurrent disease [1,2]. Germline RET testing is recommended in patients with MTC, including those without an apparent family history, because apparently sporadic disease may represent unrecognized hereditary MTC [1,2].

Tuberculosis can create an important diagnostic confounder during MTC surveillance. A tuberculous thyroid bed abscess mimicking recurrent MTC has been reported [3]. Histological coexistence of tuberculosis and MTC has also been described [4], as has MTC associated with tuberculous cervical lymphadenitis mimicking nodal metastatic disease [5]. Conversely, metastatic MTC may mimic disseminated or miliary tuberculosis when pulmonary metastases present as innumerable bilateral micronodules with a random distribution, creating a miliary radiographic pattern similar to that of hematogenous tuberculosis [6].

We report a patient with high-grade, node-positive MTC associated with tuberculous cervical lymphadenitis. Postoperative surveillance was complicated by persistent biochemical abnormality, an indeterminate thyroid bed lesion, and a transient sternal scintigraphic abnormality. To preserve de-identification and follow the journal's requested format, the date of surgery was designated Day 1, and subsequent events are reported relative to that date.

Case Presentation

A 61-year-old woman presented with a cervical swelling that had progressively increased over approximately eight months. Her relevant medical history included previously treated cervical tuberculous lymphadenitis. She had no known family history of MTC, pheochromocytoma, primary hyperparathyroidism, or multiple endocrine neoplasia.

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Preoperative thyroid ultrasonography demonstrated a multinodular goiter containing a nodule classified as European Thyroid Imaging Reporting and Data System (EU-TIRADS) category 4 according to the European Thyroid Association classification (Figure *1*) [7]. Based on the multinodular thyroid appearance, the intermediate-risk sonographic features of the nodule, and the patient's history of cervical tuberculous lymphadenitis, the main preoperative differential diagnoses included benign multinodular goiter, differentiated thyroid carcinoma, and recurrent cervical tuberculous lymphadenitis. MTC had not been established preoperatively. No preoperative serum calcitonin measurement was available, and no additional preoperative investigation specifically directed toward confirming MTC or recurrent cervical tuberculosis was documented.

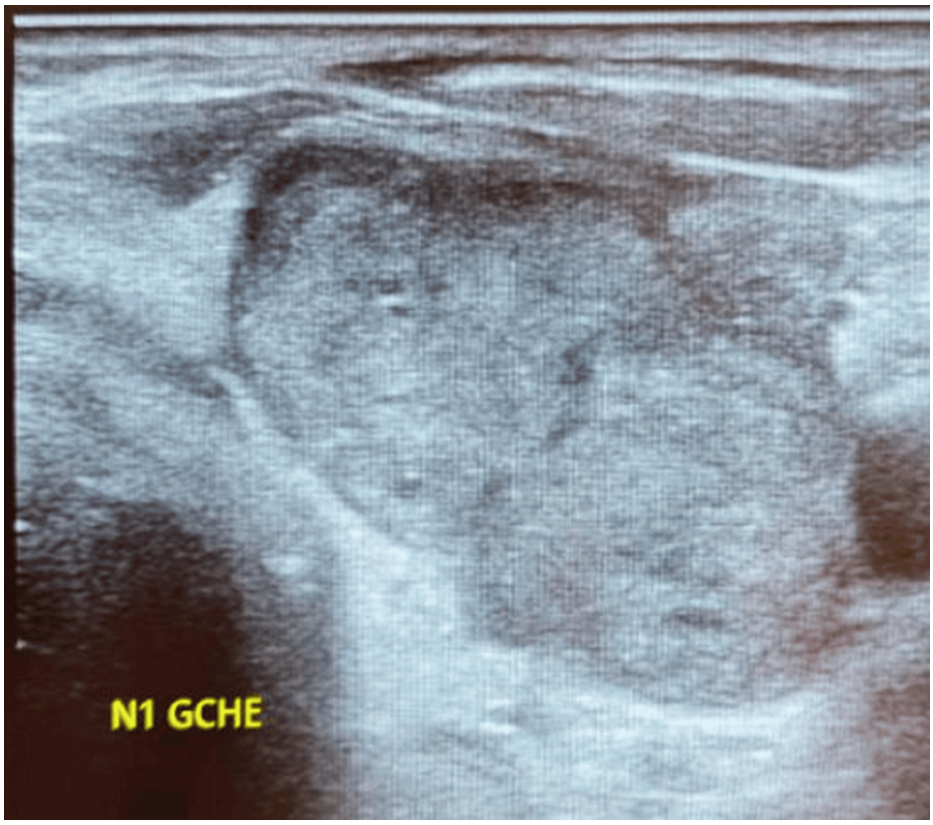


FIGURE 1: Preoperative thyroid ultrasonography showing the left thyroid nodule subsequently classified as European Thyroid Imaging and Reporting System (EU-TIRADS) category 4.

On Day 1, the patient underwent total thyroidectomy with bilateral cervical lymph node dissection. Histopathological examination unexpectedly revealed multifocal MTC with regional lymph node metastases, reported as pT4aN1a. Immunohistochemistry demonstrated diffuse and strong calcitonin expression in the tumor cells (Figure *2*). No tumor necrosis was identified, and the Ki-67 proliferation index was 35%. According to the International Medullary Thyroid Carcinoma Grading System, the tumor fulfilled the criteria for high-grade MTC [8].

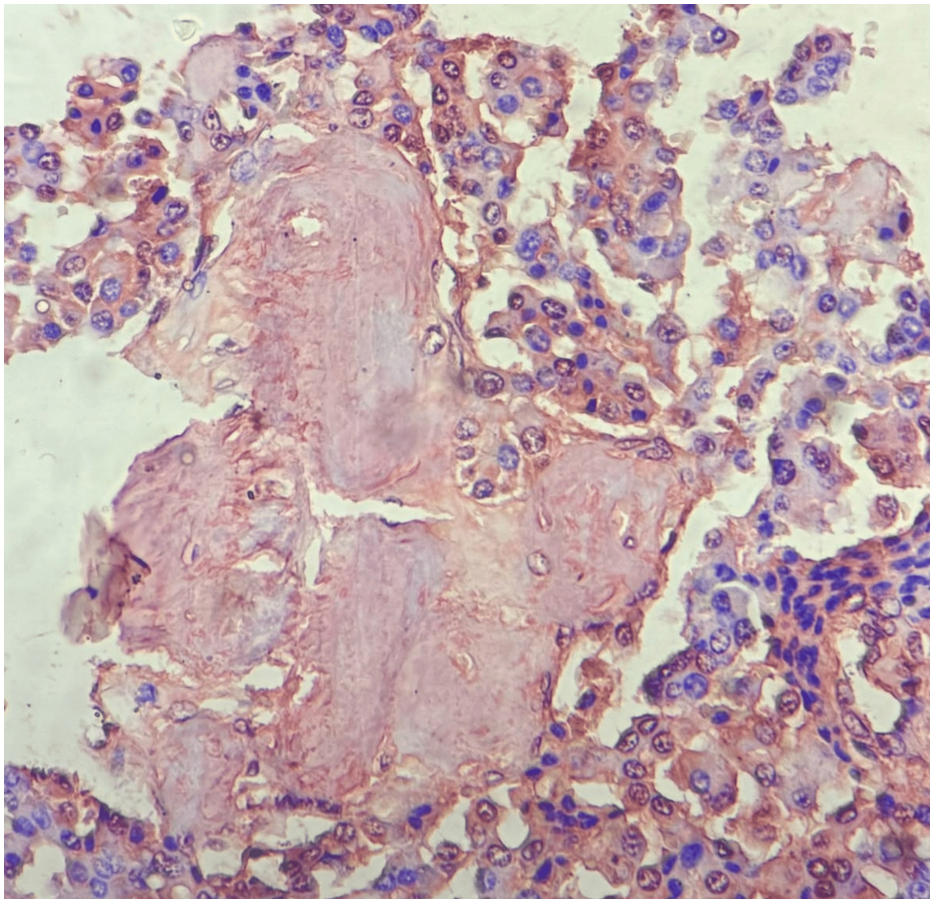


FIGURE 2: Medullary thyroid carcinoma showing diffuse and strong calcitonin immunoreactivity in tumor cells (immunohistochemistry).

Histological examination of cervical lymph node tissue additionally demonstrated epithelioid granulomatous inflammation with multinucleated giant cells and caseous necrosis (Figure *3*). Tuberculous etiology was supported by a positive Xpert MTB/RIF (GeneXpert) assay, which has established diagnostic utility in lymph node tuberculosis [9]. The available pathological documentation did not establish whether metastatic MTC and tuberculous granulomatous inflammation coexisted within the same individual lymph node.

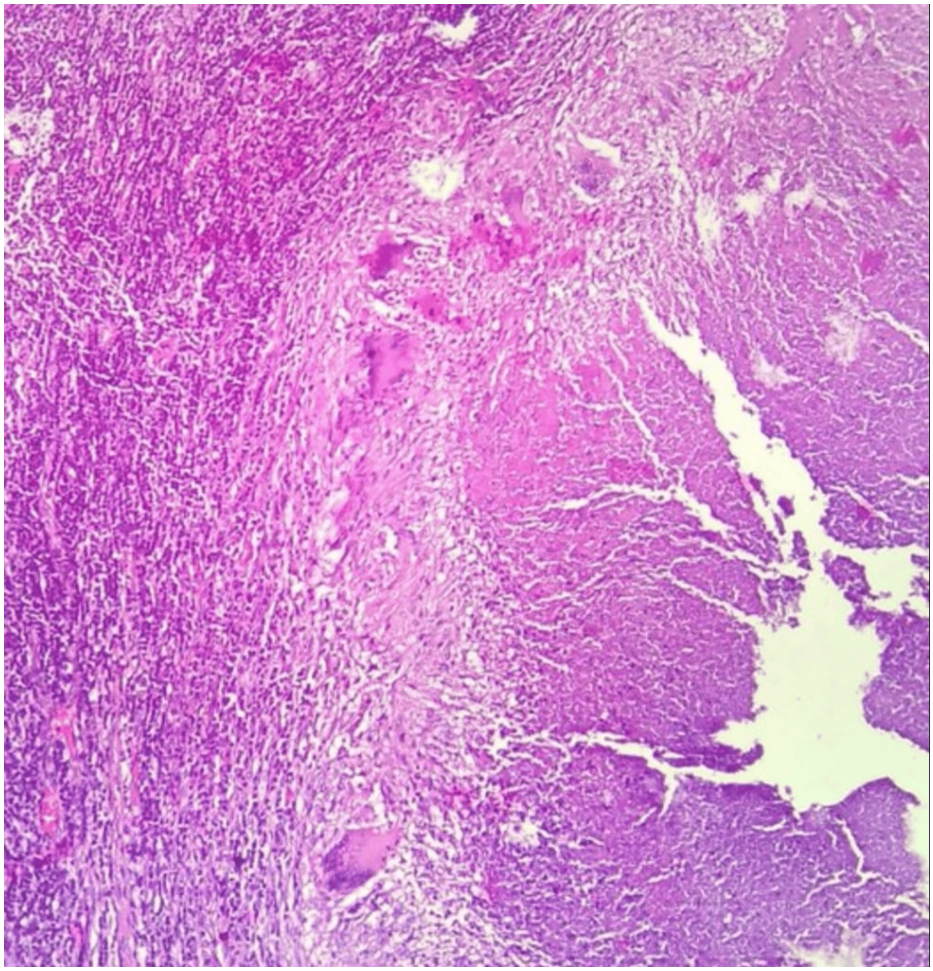


FIGURE 3: Cervical lymph node tissue showing epithelioid granulomatous inflammation with multinucleated giant cells and caseous necrosis (hematoxylin and eosin, ×100).

Postoperative biochemical assessment

The first available postoperative tumor marker assessment showed markedly increased serum calcitonin and CEA. Calcitonin remained elevated at the intermediate assessment but subsequently decreased substantially, whereas the latest CEA value returned to the laboratory reference range. All sequential calcitonin measurements were performed using the same analytical method. Quantitative results and laboratory reference ranges are summarized in Table *1*.

Analyte	Postoperative timing	Result	Reference range	Interpretation
Calcitonin	Day 64	440 ng/L	<10 ng/L	Increased
CEA	Day 75	20.6 ng/mL	<5.30 ng/mL	Increased
Calcitonin	Approximately Day 400	300 ng/L	<10 ng/L	Increased
Calcitonin	Latest follow-up	32.1 ng/L	<10 ng/L	Increased
CEA	Latest follow-up	4.67 ng/mL	<5.30 ng/mL	Within reference range

TABLE 1: Postoperative tumor-marker measurements and laboratory reference ranges.

The exact sampling day of the intermediate and latest follow-up measurements was not available; therefore, no unsupported calendar date was introduced.

CEA, carcinoembryonic antigen

Postoperative structural assessment

On Day 85, whole-body bone scintigraphy demonstrated intense focal tracer uptake in the left aspect of the manubrium sterni, initially raising concern for osseous metastatic involvement (Figure *4*). Other foci were interpreted as degenerative. CT performed on Day 111 did not demonstrate a corresponding destructive sternal lesion.

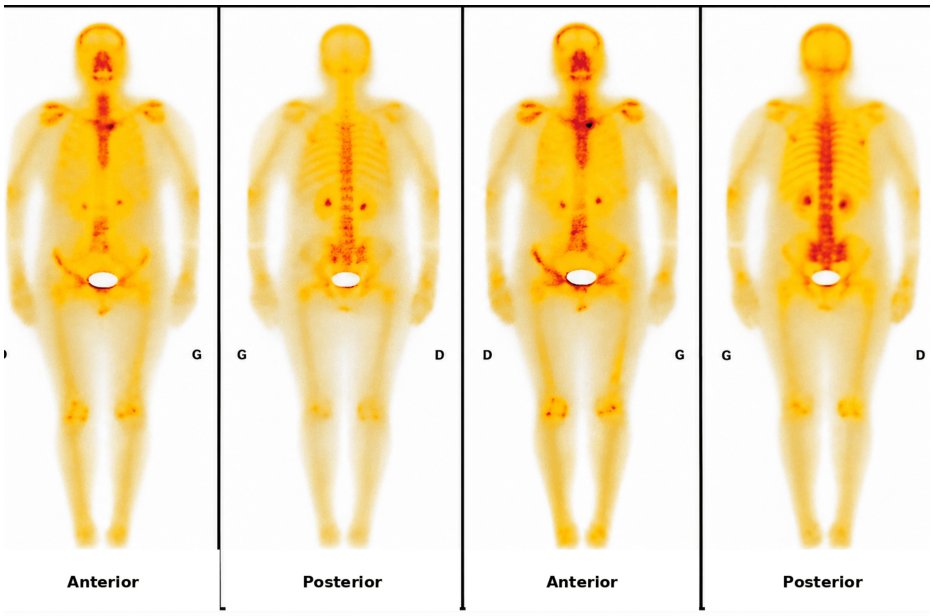


FIGURE 4: Whole-body bone scintigraphy showing focal increased tracer uptake in the left aspect of the manubrium sterni, initially raising concern for osseous metastatic involvement.

Other foci were interpreted as degenerative.

On Day 117, neck ultrasonography demonstrated morphologically suspicious right lateral cervical lymph nodes at levels II and V, together with a hypoechoic soft tissue lesion in the left thyroidectomy bed (Figure *5*). According to the corresponding ultrasound report, the largest suspicious right lateral lymph nodes measured 14.6 × 5.8 mm at level II and 11.5 × 8.3 mm at level V. Their metastatic nature was not pathologically confirmed.

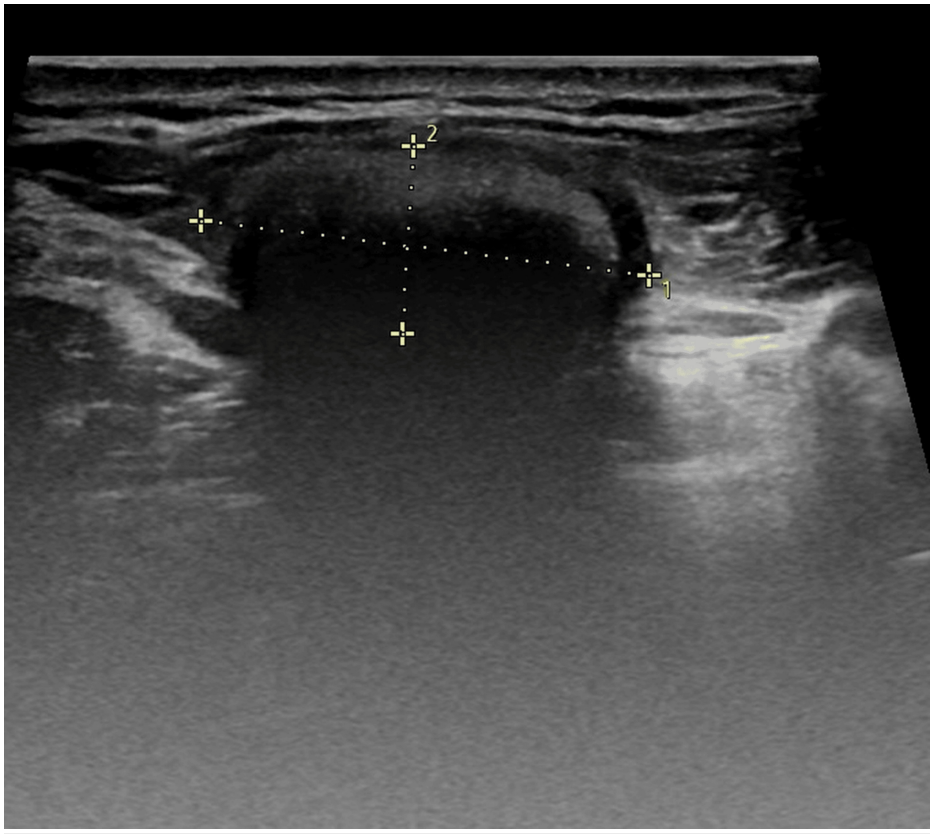


FIGURE 5: Postoperative neck ultrasonography showing a morphologically suspicious right lateral cervical lymph node.

According to the corresponding ultrasound report, suspicious right lateral cervical lymph nodes were identified at levels II and V.

At approximately Day 400, follow-up neck ultrasonography showed a small, well-defined left paratracheal thyroid bed lesion and two nonspecific cervical lymph nodes. CT of the neck, chest, abdomen, and pelvis performed on Day 453 did not demonstrate convincing progressive locoregional or distant metastatic disease. Repeat bone scintigraphy on Day 513 showed decreased intensity of the previously observed sternal uptake, without new suspicious skeletal lesions.

FDG-PET/CT and evaluation of the thyroid bed lesion

On Day 547, 18F-fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT) demonstrated a 10 × 8 mm left basicervical lesion in the thyroidectomy bed with moderate metabolic activity (SUVmax 3.08) (Figure *6*). No other suspicious hypermetabolic cervical or mediastinal lymph nodes were identified. No suspicious distant hypermetabolic focus was observed, and, importantly, there was no abnormal FDG uptake in the sternum or elsewhere in the explored skeleton.

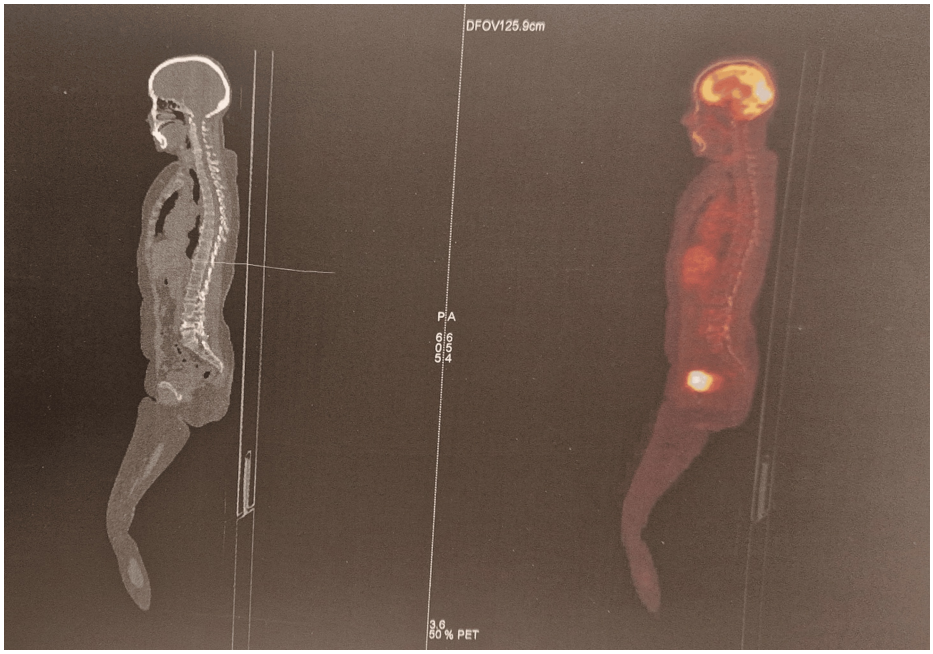


FIGURE 6: Sagittal 18F-FDG PET/CT images obtained during postoperative surveillance.

The corresponding PET/CT report described a 10 × 8 mm left basicervical lesion in the thyroidectomy bed with moderate metabolic activity (SUVmax 3.08), with no suspicious hypermetabolic uptake in the sternum or elsewhere in the explored skeleton.

18F-FDG, 18F-fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography

Because the cervical lesion remained indeterminate, ultrasound-guided fine-needle aspiration was subsequently performed together with calcitonin measurement in the needle washout. Both assessments were inconclusive. Calcitonin measurement in fine-needle aspiration washout can improve the diagnostic assessment of cervical lesions suspected of MTC involvement [10,11]; however, an inconclusive result cannot establish persistent or recurrent structural disease. The lesion was therefore considered indeterminate rather than proven recurrent MTC (Table 2). The postoperative calcitonin trajectory is illustrated in Figure 7.

Postoperative timing	Key structural finding
Day 1	Total thyroidectomy with bilateral cervical lymph-node dissection
Day 85	Focal manubrial uptake on bone scintigraphy
Day 111	CT showed no corresponding destructive sternal lesion
Day 117	Suspicious right level II and V lymph nodes and a left thyroid-bed lesion on ultrasonography
Approximately Day 400	Small left paratracheal thyroid-bed lesion on ultrasonography
Day 453	CT showed no convincing progressive locoregional or distant metastatic disease
Day 513	Regression of the sternal scintigraphic abnormality; no new suspicious skeletal lesions
Day 547	FDG-PET/CT showed a moderately avid left thyroid-bed lesion and no suspicious sternal or distant uptake
Subsequent assessment	Fine-needle aspiration cytology and calcitonin washout were inconclusive

TABLE 2: Key postoperative structural assessments, with Day 1 defined as the date of surgery.

FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography

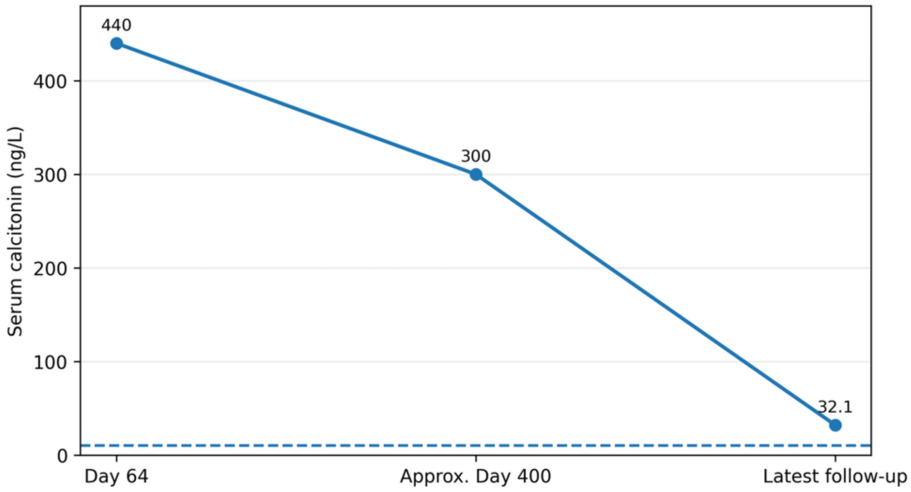


FIGURE 7: Postoperative serum calcitonin trend demonstrating a marked decrease during follow-up.

The dashed horizontal line represents the laboratory upper reference limit of 10 ng/L. All measurements were performed using the same analytical method.

Taken together, these postoperative findings remained diagnostically indeterminate: the suspicious cervical lymph nodes were not pathologically confirmed as metastatic, the persistent thyroid-bed lesion was not confirmed as recurrent MTC by cytology or calcitonin washout, and the sternal scintigraphic abnormality was not corroborated by CT and subsequently regressed on follow-up imaging.

Germline RET analysis

Germline molecular analysis of RET was performed on genomic DNA extracted from peripheral blood using polymerase chain reaction amplification followed by sequencing of exons 10, 11, 13, 15, and 16. A heterozygous pathogenic c.1858T>C variant in exon 10, resulting in the p.Cys620Arg (C620R) substitution, was identified. Biochemical screening for pheochromocytoma was negative, and serum calcium was within the reference range. Genetic counseling and targeted testing of at-risk relatives were recommended.

Discussion

This case illustrates the diagnostic challenges created by the coexistence of MTC and tuberculous cervical lymphadenitis, two conditions capable of producing overlapping cervical and imaging abnormalities. The principal challenges were to distinguish tuberculous cervical lymphadenitis from nodal metastatic MTC, to interpret a persistent thyroid-bed lesion that remained indeterminate after inconclusive cytology and calcitonin washout, and to assess an initially suspicious sternal scintigraphic abnormality that was not confirmed by CT or FDG-PET/CT and subsequently regressed. These structural uncertainties also had to be interpreted in the context of high-grade histopathology despite a marked postoperative decline in calcitonin and normalization of CEA. Thus, the central diagnostic challenge was determining which postoperative findings could reliably be attributed to persistent or metastatic MTC and which could reflect concomitant granulomatous disease or nonspecific imaging abnormalities.

MTC and tuberculous lymphadenitis

Tuberculosis has previously been reported to mimic recurrent MTC. Allan et al. described a tuberculous abscess of the thyroid bed that was initially considered recurrent MTC [3]. Channa et al. reported histological coexistence of MTC and thyroid tuberculosis [4]. Kharkwal et al. described MTC with tuberculous cervical lymphadenitis in which suspicious lateral neck nodes were tuberculous rather than metastatic [5]. The reverse diagnostic problem has also been reported, with metastatic MTC producing a miliary radiological pattern suggestive of tuberculosis [6].

In the present patient, both processes were independently supported. MTC was established by thyroid histopathology, regional lymph-node metastases, and diffuse calcitonin immunoreactivity, whereas tuberculosis was supported by caseating granulomatous lymphadenitis and a positive molecular assay. Xpert MTB/RIF has high specificity and useful sensitivity for lymph-node tuberculosis, strengthening the microbiological support for the diagnosis in an appropriate clinicopathological context [9]. Accordingly, neither process could reasonably be assumed to explain every subsequent imaging abnormality.

High-grade pathology versus longitudinal disease behavior

The tumor had adverse pathological features, including reported pT4aN1a disease and a markedly elevated Ki-67 proliferation index. The International Medullary Thyroid Carcinoma Grading System classifies MTC as high grade when any of the following is present: a mitotic index of at least five per 2 mm^2, a Ki-67 index of at least 5%, or tumor necrosis [8]. Thus, the Ki-67 finding alone established high-grade disease despite the absence of tumor necrosis. High-grade MTC is associated with less favorable locoregional recurrence-free, distant metastasis-free, disease-specific, and overall survival than low-grade MTC [8]. Nevertheless, histological grade should not be interpreted as synonymous with inevitable short-term structural progression in an individual patient.

Interpretation of the cervical abnormalities

The persistent left thyroid-bed lesion was detected by several modalities. Small differences in measured dimensions should not be interpreted as definite growth or regression because the measurements were obtained using different imaging techniques and planes. Moderate FDG uptake is not specific for recurrent MTC, and 18F-FDG PET has limited sensitivity in some patients with MTC, particularly at lower calcitonin concentrations [12].

Fine-needle aspiration with calcitonin measurement in needle washout can substantially improve diagnostic sensitivity for suspicious MTC lesions compared with cytology alone [10,11]. In the present case, however, both investigations were inconclusive. The lesion should therefore remain classified as indeterminate rather than being labeled residual or recurrent carcinoma. Similarly, the morphologically suspicious lateral cervical lymph nodes were not pathologically confirmed as metastatic and therefore do not alter the reported pathological nodal stage.

Sternal abnormality

The initial manubrial uptake on bone scintigraphy was concerning in the context of node-positive MTC and elevated postoperative tumor markers. However, CT did not show a corresponding destructive lesion, the scintigraphic abnormality decreased on follow-up, and subsequent FDG-PET/CT demonstrated no abnormal sternal metabolism. The most rigorous interpretation is therefore an initially suspicious but unconfirmed sternal scintigraphic abnormality.

Conversely, there is insufficient evidence to classify it as osseous tuberculosis because no tissue or microbiological confirmation was obtained from the sternum. This distinction is central to the educational value of the case: a proven malignancy should not lead to automatic malignant attribution of every imaging abnormality, especially when a concomitant granulomatous disease is present.

Postoperative tumor marker kinetics

The serial measurements demonstrated a marked postoperative decline in calcitonin and normalization of CEA, as shown in Table *1* and Figure *7*. Because all calcitonin measurements were obtained using the same analytical method, inter-assay variability is unlikely to explain the magnitude of the trend.

Postoperative calcitonin generally normalizes rapidly after complete tumor removal, although the interval to normalization is influenced by tumor burden and nodal disease, and delayed normalization has been described [13,14]. The present trajectory is best described as substantial postoperative biochemical improvement rather than a treatment response because no additional anticancer intervention occurred during the period of decline. Calcitonin and CEA doubling times are established prognostic tools when markers are rising, but calculation is not appropriate for a clearly downward trajectory and requires sufficient serial measurements [15]. Continued biochemical and ultrasound surveillance remains warranted because calcitonin remains above the laboratory reference range and the cervical lesion remains indeterminate.

Significance of the germline RET C620R variant

Germline RET testing was appropriate despite the absence of a known family history. The American Thyroid Association (ATA) and European Society for Medical Oncology (ESMO) guidelines recommend RET testing in patients with MTC because apparently sporadic disease may represent unrecognized hereditary MTC [1,2]. Pathogenic cysteine-domain RET variants are associated with MEN2A and familial MTC [16], and the p.Cys620Arg substitution at codon 620 was specifically reported in affected MEN2A and familial MTC families [17]. Because the variant was identified in peripheral-blood genomic DNA, it establishes a hereditary RET-associated form of MTC in this patient. The finding warrants genetic counseling, targeted testing of at-risk relatives, and continued surveillance for MEN2-associated manifestations.

Limitations

This report has several limitations. MTC was diagnosed unexpectedly after surgery, and a preoperative calcitonin concentration was unavailable. The available pathological documentation did not establish

whether metastatic MTC and tuberculous granulomas occurred within the same individual lymph node. In addition, the persistent thyroid-bed lesion could not be definitively characterized because both cytology and calcitonin washout were inconclusive. These limitations do not alter the central observation that longitudinal interpretation required integration of malignant, infectious, biochemical, genetic, and imaging data.

Conclusions

The coexistence of high-grade medullary thyroid carcinoma and tuberculous cervical lymphadenitis can create substantial diagnostic uncertainty during postoperative surveillance. In this patient, both disorders were independently supported by pathological and microbiological findings, while subsequent cervical and skeletal abnormalities remained insufficiently specific to be automatically attributed to metastatic disease.

Tumor markers improved markedly during follow-up, no progressive distant structural disease was demonstrated, the persistent thyroid-bed lesion remained indeterminate, and the initially suspicious sternal scintigraphic abnormality regressed without morphologic or metabolic confirmation of metastasis. The additional identification of a pathogenic germline RET C620R variant established hereditary RET-associated MTC and has direct implications for the patient and her relatives. This case underscores the importance of integrating pathology, microbiology, molecular genetics, serial tumor markers, and longitudinal imaging to avoid both overdiagnosis and undertreatment during postoperative MTC surveillance.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Lahoussaine Abainou, Ali Halouache, Moad Bellaoui, Mohamed Amine Sas, Mohammed Tbouda

Acquisition, analysis, or interpretation of data: Lahoussaine Abainou, Ali Halouache, Moad Bellaoui, Mohamed Amine Sas, Mohammed Tbouda

Drafting of the manuscript: Lahoussaine Abainou

Critical review of the manuscript for important intellectual content: Lahoussaine Abainou, Ali Halouache, Moad Bellaoui, Mohamed Amine Sas, Mohammed Tbouda

Supervision: Lahoussaine Abainou, Ali Halouache

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. N/A issued approval N/A. Written informed consent was obtained from the patient for publication of the case details and accompanying images. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received 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 have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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