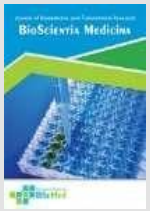
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Metastatic Medullary Thyroid Carcinoma Mimicking a Primary Soft Tissue Sarcoma of the Shoulder: A Case Report

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ARTICLE INFO

Keywords:
Immunohistochemistry
Medullary thyroid carcinoma
RET proto-oncogene
Sarcoma
Soft tissue metastasis

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i1.1495

A B S T R A C T

Background: Medullary thyroid carcinoma (MTC) is a rare neuroendocrine malignancy accounting for 1-5% of thyroid cancers. While often presenting with cervical lymphadenopathy, distant metastasis to bone and soft tissue mimicking a primary sarcoma is exceptionally rare. This report details a case of MTC where the primary diagnostic challenge was a massive, destructive shoulder mass. **Case presentation:** A 58-year-old woman presented with a disabling, 20 cm mass in her left shoulder, progressively enlarging over two years. The patient also noted a 30-year history of a stable, asymptomatic neck lump. Magnetic Resonance Imaging (MRI) revealed a large, hypervascular, destructive mass obliterating the scapula and invading surrounding musculature, with a radiological differential diagnosis of a primary soft tissue sarcoma. Laboratory investigation, however, revealed a massively elevated serum calcitonin (>2000 pg/mL) and carcinoembryonic antigen (CEA) (180 ng/mL). A CT-guided core biopsy of the shoulder mass, initially suspected to be a sarcoma, was negative for all sarcoma markers. Instead, it was strongly positive for neuroendocrine (Synaptophysin, Chromogranin A) and thyroid-specific (TTF-1, PAX-8) markers, as well as definitive MTC markers (Calcitonin, CEA). This confirmed the diagnosis of metastatic MTC. Staging was completed as pT3a pN1b M1. The patient underwent total thyroidectomy with bilateral central and left modified radical neck dissection, followed by planned palliative resection of the shoulder metastasis and systemic therapy with a selective RET inhibitor. **Conclusion:** This case highlights a critical diagnostic pitfall. Metastatic MTC can present as a massive soft tissue neoplasm mimicking a primary sarcoma. In such cases, a systematic diagnostic approach combining serum biomarkers (Calcitonin, CEA) with a comprehensive immunohistochemical panel is essential to establish the correct diagnosis and initiate appropriate, life-extending targeted therapy.

1. Introduction

Thyroid malignancies represent the most common endocrine cancer, with a globally increasing incidence. These cancers are, however, a heterogeneous group, ranging from the highly prevalent and indolent papillary thyroid carcinomas (PTC) to the lethal and rapidly progressive anaplastic thyroid carcinoma (ATC).[1] Occupying a unique position within this spectrum is medullary thyroid carcinoma (MTC). MTC is a neuroendocrine neoplasm that originates from the parafollicular C-cells of the thyroid gland, which are embryologically derived from the neural crest.[2] These C-cells are responsible for the synthesis and secretion of calcitonin, a peptide hormone involved in calcium homeostasis, which also serves as the pathognomonic serum tumor marker for MTC.[3]

MTC is a rare entity, accounting for approximately 1-5% of all thyroid cancers. It exists in two distinct clinical forms: a sporadic form, which is unifocal and accounts for 75-80% of cases, and a hereditary form

(20-25%) that presents as part of the Multiple Endocrine Neoplasia (MEN) type 2A or 2B syndromes, or as Familial MTC (FMTC).[4] Both forms are predominantly driven by gain-of-function mutations in the RET proto-oncogene. In hereditary MTC, a germline RET mutation is present in virtually all cases, with specific codons (such as Cys634 in MEN2A or Met918Thr in MEN2B) dictating the phenotype. In sporadic MTC, somatic RET mutations are found in 50-60% of tumors, with the aggressive M918T mutation being the most common.[5] A smaller subset of sporadic MTCs lacking RET mutations may be driven by somatic mutations in RAS genes, such as HRAS or KRAS.

The clinical behavior of MTC differs significantly from that of differentiated thyroid cancer. MTC does not uptake iodine, rendering radioactive iodine therapy ineffective. It demonstrates a much higher propensity for early lymphatic and hematogenous spread.[6] At the time of initial diagnosis, 50-70% of patients already have metastases to the cervical lymph nodes, and approximately 10-15% present with distant metastatic disease. The most common sites of distant spread are the liver, lungs, and bone.

Bone metastases from MTC typically manifest as osteolytic or mixed lytic-sclerotic lesions, often causing pain or pathological fractures.[7] However, the presentation of MTC as a massive, primary soft-tissue mass with extensive bone destruction, thereby mimicking a high-grade soft tissue sarcoma, is an exceptionally rare and diagnostically challenging scenario. Soft tissue metastases from any primary carcinoma are uncommon, and those from MTC are relegated to a handful of case reports, often involving locations like the gluteal muscles or thigh.[8] A massive metastasis to the shoulder girdle, completely obliterating the scapula and presenting as the patient's chief complaint, represents a significant diagnostic pitfall. Such a presentation can easily lead to a misdiagnosis of a primary musculoskeletal malignancy, potentially resulting in inappropriate surgical management (such as a radical limb-sparing resection or amputation) before the systemic nature of the disease is recognized.[9]

This case report details the sophisticated diagnostic journey of a 58-year-old woman who presented to our surgical oncology unit with a disabling, massive shoulder mass, initially diagnosed by external imaging as a probable soft tissue sarcoma. We describe the sequential clinical, serological, radiological, and pathological investigations that unraveled the true diagnosis of a sporadic, RET-mutated medullary thyroid carcinoma with synchronous pulmonary and massive scapular metastases originating from a long-standing, seemingly-indolent primary thyroid tumor.[10] The aim of this report is to highlight this atypical metastatic pathway of MTC, to emphasize the critical, step-wise diagnostic algorithm necessary to differentiate this carcinoma-mimic from a true sarcoma, and to discuss the pathophysiology and molecular mechanisms that may underpin such an aggressive and unusual metastatic phenotype. The novelty of this case lies in its extreme presentation, which serves as a crucial clinical lesson for oncologists, surgeons, radiologists, and pathologists.

2. Case Presentation

A 58-year-old woman was referred to the Surgical Oncology clinic at Dr. Hasan Sadikin General Hospital with the chief complaint of a large, painful, and progressively enlarging lump on her left shoulder, first noticed two years prior. The patient also reported a 30-year history of a lump in the left side of her neck. This neck lump had been asymptomatic and largely stable in size for three decades, leading her to believe it was benign.

The shoulder complaint began approximately 24 months prior to presentation as a dull ache, which was intermittently treated with analgesics. A small, firm nodule was palpated by the patient 18 months ago. Over the last six months, this shoulder mass underwent rapid, exponential growth, evolving into a massive, disabling lesion that severely restricted her daily activities. This was associated with progressive pain and a new-onset paresthesia over the lateral

aspect of her arm.

Her past medical and surgical history was unremarkable. She had no personal or family history of thyroid cancer, parathyroid hyperplasia, or pheochromocytoma. She specifically denied symptoms of carcinoid syndrome, such as flushing or chronic diarrhea. On review of systems, she reported no dysphagia, odynophagia, hoarseness, or dyspnea.

On physical examination, the patient was well-appearing, in no acute distress. Her vital signs were stable: blood pressure 120/80 mmHg, heart rate 78 beats/min, respiratory rate 16 breaths/min, and temperature 36.5°C. Her Eastern Cooperative Oncology Group (ECOG) performance status was 1, limited only by the mechanical burden of the shoulder mass. Head and neck examination revealed a large, firm, non-tender mass in the left lobe of the thyroid, measuring approximately 7 x 5 cm. The mass was mobile with swallowing and not fixed to the overlying skin or strap muscles. There was no palpable cervical lymphadenopathy on initial examination (Table 1).

Examination of the left shoulder was remarkable. There was a massive, 20 x 15 x 10 cm, hard, immobile mass completely encompassing the posterior and lateral aspects of the shoulder. The mass was fixed to the underlying skeletal structures. The overlying skin was tense, shiny, and erythematous, with prominent, dilated superficial veins. The mass was non-pulsatile, and no bruit was appreciated. The active range of motion of the left shoulder was severely limited: 20 degrees of flexion, 10 degrees of abduction, and minimal internal/external rotation. Passive range of motion was similarly restricted and painful. Neurological examination of the left upper extremity revealed hypoesthesia in the C5 dermatome (lateral arm) but intact motor function (5/5) in the biceps, triceps, and wrist/hand extensors and flexors, suggesting nerve irritation rather than transection. Respiratory and abdominal examinations were normal, with no hepatomegaly.

Initial laboratory workup included a complete blood count (CBC) and a comprehensive metabolic panel (CMP). The CBC was within normal limits. The CMP was notable for a slightly elevated alkaline phosphatase (ALP) of 150 U/L (reference range: 44-147 U/L), suggesting increased osteoblastic activity or bone turnover. Serum calcium was normal at 9.2 mg/dL. Renal and hepatic function tests were otherwise unremarkable. A thyroid function panel was ordered to evaluate the neck mass, revealing a euthyroid state: Thyroid Stimulating Hormone (TSH) 1.5 mU/L (ref: 0.4-4.2), free Thyroxine (fT4) 1.2 ng/dL (ref: 0.8-1.8), and total Triiodothyronine (T3) 1.1 ng/mL (ref: 0.8-2.0). Thyroglobulin (Tg) and anti-thyroid peroxidase (anti-TPO) antibodies were undetectable. Given the neuroendocrine features of MTC, specific tumor markers were requested. The results were pathognomonic: (1) Serum Calcitonin: > 2000 pg/mL (reference range: < 10 pg/mL); (2) Serum Carcinoembryonic Antigen (CEA): 180 ng/mL (reference range: < 5 ng/mL for non-smokers). These massively elevated markers, particularly the calcitonin, confirmed a diagnosis of MTC and indicated a very high tumor burden, even before all imaging was complete. A high-resolution ultrasound of the neck demonstrated a 7.5 x 5.1 x 4.8 cm, solid, hypoechoic, irregular-bordered mass with prominent intranodular macrocalcifications, replacing the entirety of the left thyroid lobe. This was classified as a TI-RADS 5 (Thyroid Imaging Reporting and Data System) lesion, highly suspicious for malignancy. The right thyroid lobe and isthmus were unremarkable. The ultrasound also revealed several suspicious lymph nodes in the left lateral neck (Level IV), the largest measuring 1.2 cm with a round shape and loss of the fatty hilum. An MRI of the left shoulder with and without gadolinium contrast was performed to evaluate the primary complaint.

Table 1. Clinical Findings of the Patient on Admission

CATEGORY	FINDING	DETAILS
Demographics	Age	58 years
Sex	Female	
History of Present Illness	Chief Complaint	Large, painful, progressively enlarging mass on left shoulder
Duration	First noticed 2 years prior	
Progression	Rapid, exponential growth over the last 6 months	
Associated Symptoms	Progressive pain; new-onset paresthesia over the lateral aspect of the arm (C5 dermatome)	
Past & Family History	Primary Neck Lump	30-year history of a lump in the left side of the neck; reported as asymptomatic and stable
Past Medical/Surgical Hx	Unremarkable	
Family History (MEN)	No family history of thyroid cancer, parathyroid hyperplasia, or pheochromocytoma	
Review of Systems	Denied flushing, chronic diarrhea, dysphagia, odynophagia, hoarseness, or dyspnea	
Physical Examination	Vitals & Performance	Stable (BP 120/80, HR 78, RR 16, Temp 36.5°C); ECOG Performance Status: 1
Neck Examination	7 × 5 cm, firm, non-tender mass in the left lobe of the thyroid; mobile with swallowing	
Shoulder Mass	20 × 15 × 10 cm, hard, immobile mass fixed to underlying skeletal structures	
Overlying Skin (Shoulder)	Tense, shiny, and erythematous with prominent, dilated superficial veins	
Shoulder Function	Severely limited active (Flex 20°, Abd 10°) and passive range of motion; Neurological: Hypoesthesia in C5 dermatome, motor function 5/5	
Laboratory & Serology	Metabolic Panel	Alkaline Phosphatase (ALP): 150 U/L (Ref: 44-147 U/L) (Slightly Elevated); Serum Calcium: 9.2 mg/dL (Normal)
Thyroid Function	Euthyroid State: TSH 1.5 mU/L, fT4 1.2 ng/dL, T3 1.1 ng/mL (All Normal)	
Tumor Marker: Calcitonin	**> 2000 pg/mL (Ref: < 10 pg/mL) (Massively Elevated)**	
Tumor Marker: CEA	**180 ng/mL (Ref: < 5 ng/mL) (Massively Elevated)**	

The study revealed a massive, infiltrative, and destructive neoplastic process; (1) T1-weighted images showed a large, 20.1 x 14.8 x 10.3 cm mass, predominantly isointense to muscle, replacing the normal anatomy of the shoulder girdle; (2) T2-weighted images (fat-suppressed) demonstrated heterogeneous high signal intensity, indicative of a hypercellular tumor with areas of internal necrosis; (3) Post-contrast T1 (fat-suppressed): The mass showed intense, avid, and heterogeneous enhancement, confirming its hypervascular nature; (3) Structural Involvement: There was gross, lytic destruction of the scapular body, spine, and acromion process. The tumor exhibited extensive extra-osseous extension,

invading the supraspinatus, infraspinatus, subscapularis, and deltoid muscles. The tumor mass was seen abutting and displacing the axillary artery, vein, and brachial plexus, but definitive neurovascular encasement was not identified. The initial radiology report concluded: "Aggressive, hypervascular malignant neoplasm with extensive bone destruction and a massive soft tissue component. The findings are highly suspicious for a primary high-grade soft tissue sarcoma (such as undifferentiated pleomorphic sarcoma, angiosarcoma, or synovial sarcoma) or, less likely, a solitary, aggressive metastasis."

A contrast-enhanced Computed Tomography (CT) of the neck, chest, abdomen, and pelvis was performed for systemic staging; (1) Neck: Confirmed the 7.5 cm left thyroid mass and the 1.2 cm left Level IV lymph node; (2) Chest: Confirmed the destructive scapular mass. Critically, it also revealed multiple bilateral pulmonary nodules, consistent with "cannonball" metastases. The largest nodule measured 1.5 cm in the right lower lobe. There was no mediastinal adenopathy or pleural effusion; (3) Abdomen/Pelvis: No evidence of hepatic, adrenal, or other visceral or osseous metastases.

Given the competing diagnoses (Sarcoma vs. Metastasis), a CT-guided core biopsy of the massive shoulder mass was performed as the definitive diagnostic step. Concurrently, an ultrasound-guided Fine Needle Aspiration (FNAB) of the left thyroid nodule was performed; (1) Shoulder Mass Core Biopsy: Histology (H&E staining): The core biopsies were hypercellular, consisting of a diffuse infiltrate of neoplastic cells arranged in solid sheets, nests (zellballen), and trabeculae. The cells were polygonal to spindle-shaped (plasmacytoid), with moderate amounts of eosinophilic cytoplasm. The nuclei were eccentric, round-to-oval, with the characteristic "salt-and-pepper" stippled chromatin of a neuroendocrine tumor. Mitotic activity was brisk. Significantly, there were abundant deposits of acellular, eosinophilic, amorphous material in the stroma, consistent with amyloid. This was confirmed with a Congo Red stain, which demonstrated apple-green birefringence under polarized light; Immunohistochemistry (IHC): A comprehensive IHC panel was performed to resolve the differential diagnosis; (i) Sarcoma Markers: Desmin, Myogenin, S-100, SOX10, TLE1, and CD34 were all Negative; (ii) Epithelial/Carcinoma Markers: Pan-Cytokeratin (AE1/AE3) and CK7 were strongly Positive. CK20 was Negative; (iii) Thyroid-Specific Markers: TTF-1 and PAX-8 were both diffusely and strongly Positive (nuclear staining), confirming a thyroid primary; (iv) Neuroendocrine/MTC-Specific Markers: Synaptophysin and Chromogranin A were strongly Positive (cytoplasmic). Calcitonin was diffusely, overwhelmingly Positive. Monoclonal CEA was also strongly Positive; Pathological Conclusion: "Metastatic Medullary Thyroid Carcinoma; (2) Thyroid Nodule Fine Needle Aspiration (FNAB); (i) Cytology: The smear was hypercellular, showing discohesive and loosely clustered plasmacytoid and spindle cells. The cells exhibited eccentric nuclei, granular "salt-and-pepper" chromatin, and occasional intranuclear pseudoinclusions. A background of amorphous amyloid was noted; (ii) Cytological Diagnosis: "Malignant, Medullary Thyroid Carcinoma (Bethesda Category VI). The final integrated diagnosis was: Sporadic, Medullary Thyroid Carcinoma, Stage IVC (AJCC 8th Edition) based on cT3a cN1b M1 (pulmonary and bone/soft tissue).

The patient was discussed at the multidisciplinary tumor board (MDT), involving Surgical Oncology (Head & Neck), Orthopedic Oncology, Medical Oncology, and Radiation Oncology. A multi-pronged management plan was formulated: (1) Surgical Control of Primary Tumor and Regional Disease: The patient first underwent a total thyroidectomy, bilateral central neck dissection (Level VI), and a left modified radical neck dissection (Levels II-V); (2) Systemic Therapy: Following surgical recovery, the patient was scheduled to commence systemic therapy. Given the identification of the RET M918T mutation, she was a prime candidate for a highly selective RET inhibitor, such as Selpercatinib, rather than conventional chemotherapy or older multi-kinase inhibitors (like Vandetanib); (3) Management of Shoulder Metastasis:

The massive shoulder metastasis was deemed unresectable for cure. However, due to its significant tumor burden, disabling pain, and neurological compromise, a palliative approach was planned. This consisted of an initial course of systemic therapy to achieve cytoreduction, followed by consideration for a palliative wide excision / partial scapulectomy and adjuvant External Beam Radiotherapy (EBRT) to the surgical bed (such as 50 Gy in 25 fractions) for long-term local control and symptom palliation.

The surgical procedure was performed as planned. The final histopathology report of the surgical specimen confirmed: (1) Thyroid: A 7.5 cm unifocal medullary carcinoma in the left lobe. The tumor demonstrated extensive lymphovascular invasion. It was confined to the thyroid, with no extrathyroidal extension (pT3a). Surgical margins were negative. The right lobe and isthmus were benign; (2) Lymph Nodes: Bilateral central neck dissection (Level VI) yielded 10 lymph nodes, all negative for carcinoma (0/10; pN0). The left modified radical neck dissection (Levels II-V) yielded 22 nodes, with 3 nodes in Level IV positive for metastatic MTC (3/22; pN1b); (3) Final Pathological Stage: pT3a pN1b M1.

The patient's post-operative course was uneventful. She had no hypocalcemia or recurrent laryngeal nerve palsy. She was discharged on levothyroxine. Four weeks post-operatively, her tumor markers remained elevated, as expected given the M1 disease: Serum Calcitonin was 1500 pg/mL and Serum CEA was 150 ng/mL. She was referred to Medical Oncology to initiate systemic therapy.

Table 2. Treatment, Follow-up, and Outcome

CATEGORY	COMPONENT	DETAILS
Multidisciplinary Plan	Consultation	Multidisciplinary Tumor Board (MDT) discussion (Surgical Oncology, Orthopedic Oncology, Medical Oncology, Radiation Oncology)
Primary Tumor & Regional Nodes	Total thyroidectomy + Bilateral central neck dissection (Level VI) + Left modified radical neck dissection (Levels II-V)	
Systemic Disease (M1)	Commence systemic therapy with a highly selective RET inhibitor (e.g., Selpercatinib) targeting the RET M918T mutation.	
Shoulder Metastasis (Palliative)	• Initial systemic therapy for cytoreduction. • *Followed by consideration* for palliative wide excision / partial scapulectomy + Adjuvant EBRT (e.g., 50 Gy in 25 fractions).	
Surgical Intervention & Pathology	Procedure Performed	Surgical control of primary and regional disease was performed as planned.
Pathology (Primary Tumor)	7.5 cm unifocal MTC (left lobe); Extensive lymphovascular invasion; Confined to thyroid (no extrathyroidal extension); Margins negative. **(pT3a)**	
Pathology (Lymph Nodes)	• Level VI (Central): 0/10 nodes positive (pN0). • Levels II-V (Left): 3/22 nodes positive in Level IV. **(pN1b)**	
Final Pathological Stage	**pT3a pN1b M1 (AJCC 8th Edition, Stage IVC)**	
Post-Operative Course & Follow-up	Immediate Outcome	Uneventful. No hypocalcemia. No recurrent laryngeal nerve palsy.
Disposition	Discharged on levothyroxine.	
4-Week Follow-up (Tumor Markers)	• Serum Calcitonin: 1500 pg/mL (Remains Elevated) • Serum CEA: 150 ng/mL (Remains Elevated)	
Next Step / Plan	Referred to Medical Oncology to initiate systemic (selective RET inhibitor) therapy.	

3. Discussion

This case report presents an extraordinarily rare and challenging manifestation of medullary thyroid carcinoma. The primary clinical puzzle was not the thyroid nodule, which had been indolent for three decades, but the explosive, two-year growth of a massive shoulder metastasis that radiologically and clinically mimicked a primary soft tissue sarcoma. This discussion will focus on the pathophysiology and molecular underpinnings that could lead to such an atypical metastatic presentation, and the methodological diagnostic approach required to avoid error.[11]

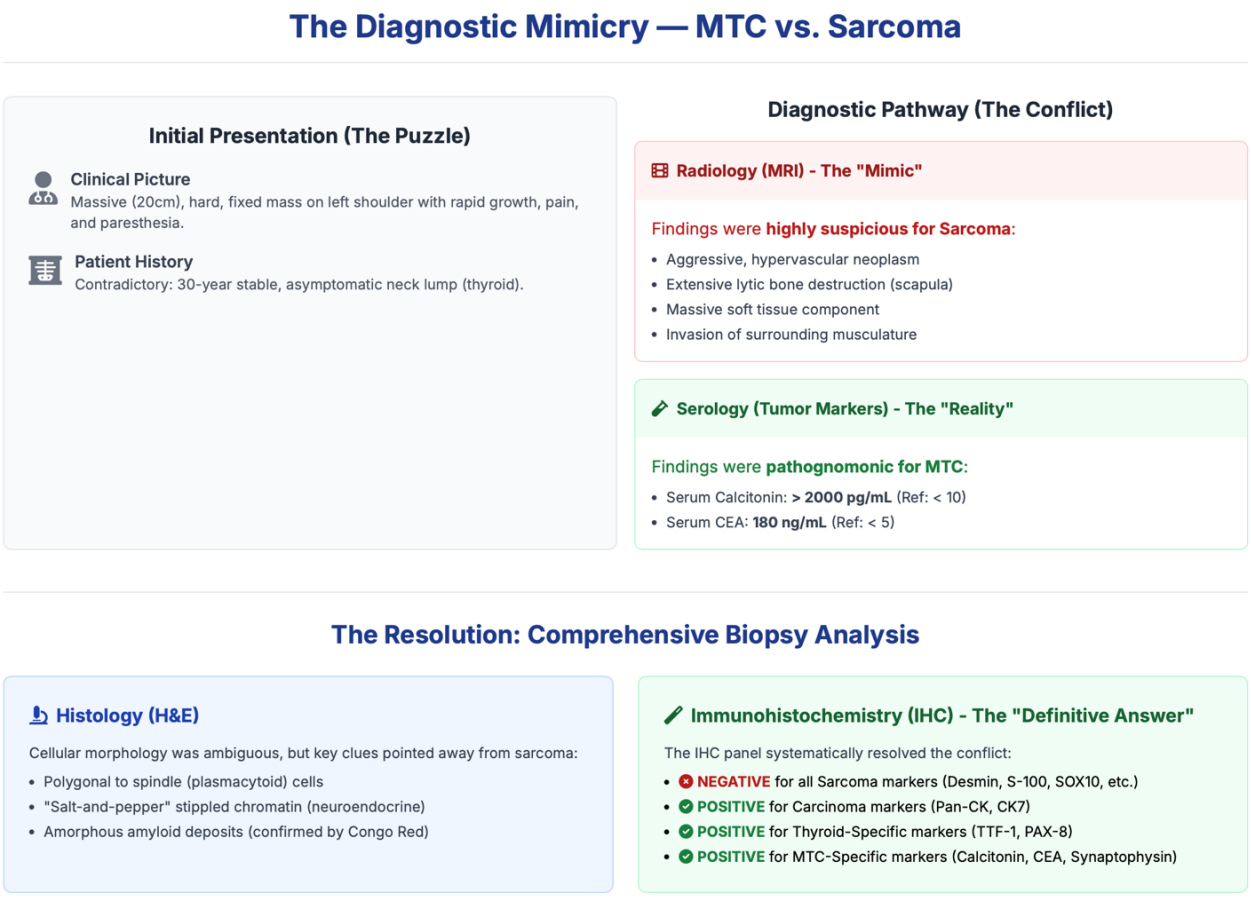

Figure 1. The diagnostic mimicry: MTC vs. sarcoma.

The initial radiological assessment, which confidently proposed a primary high-grade soft tissue sarcoma, was not an error in interpretation; rather, it was a logical and well-founded conclusion based on overwhelming visual evidence. The Magnetic Resonance Imaging (MRI) findings of a massive, 20 cm, infiltrative, and hypervascular neoplasm, characterized by profound heterogeneous enhancement, internal necrosis, and extensive lytic destruction of the scapula, are the classic, textbook hallmarks of an aggressive mesenchymal malignancy. Radiologically, this presentation creates a powerful anchoring bias. The differential diagnosis for such a lesion is narrow and grim, typically including undifferentiated pleomorphic sarcoma (UPS), angiosarcoma (given the hypervascularity), or perhaps

a synovial sarcoma, given the appendicular location.[12]

Aggressive, solitary, lytic, and hypervascular bone metastases from carcinomas are, of course, known to occur. However, the list of primary tumors that behave this way—the "great mimics" of sarcoma—is short. This differential is overwhelmingly dominated by renal cell carcinoma (RCC), which is infamous for its ability to produce such lesions, followed by lung, breast, and melanoma. A thyroid primary is seldom, if ever, a primary consideration. Medullary thyroid carcinoma (MTC), representing only 1-5% of all thyroid cancers, would be a vanishingly rare consideration for the radiologist or the orthopedic oncologist encountering this destructive shoulder mass. This rarity is the crux of the diagnostic pitfall; the clinical and radiological data pointed so strongly to one disease (sarcoma) that it threatened to obscure the path to the correct diagnosis.[13] The resolution of this profound diagnostic dilemma, therefore, rested entirely on a systematic, unbiased, and comprehensive pathological investigation. This case powerfully advocates that when faced with an undifferentiated malignant neoplasm, a narrow, hypothesis-driven immunohistochemical (IHC) panel is fraught with peril.[14] Had the pathologist, anchored by the radiological report, run a "sarcoma panel" alone (Desmin, Myogenin, S-100, SOX10, TLE1, CD34), the results would have been uniformly negative. This would have yielded a confusing and therapeutically useless diagnosis of "unclassified malignant neoplasm," or "spindle cell sarcoma, not otherwise specified."

The key to unlocking this case was the concurrent application of a broad, algorithmic IHC panel designed to test all major oncologic lineages simultaneously. The diagnostic cascade was a model of clarity: (1) The "Pivot Point" (Establishing Carcinoma): The uniform negativity of the sarcoma panel served as a hard stop to the initial hypothesis. The immediate, strong positivity for Pan-Cytokeratin (AE1/AE3) and Cytokeratin 7 (CK7) was the "pivot point." This definitively established the tumor as epithelial (a carcinoma), not mesenchymal, and instantly reframed the entire diagnostic quest from "What kind of sarcoma is this?" to "Where did this carcinoma come from?"; (2) The "Primary Hunt" (Locating the Origin): With a diagnosis of "metastatic carcinoma of unknown primary," the next tier of organ-specific markers was deployed. The dual positivity for Thyroid Transcription Factor-1 (TTF-1) and PAX-8 was the "smoking gun" for the primary site. This combination is highly specific. While TTF-1 positivity alone can suggest a lung primary, and PAX-8 positivity alone is classic for a renal cell or Müllerian primary, their concurrent expression in a carcinoma is a robust and reliable signature for a thyroid origin. This finding, in an instant, connected the "explosive" 2-year shoulder mass to the "indolent" 30-year neck lump; (3) The "Final Confirmation" (Subtyping the Tumor): The final tier of the IHC panel confirmed the precise histotype. Strong, diffuse positivity for the neuroendocrine markers Synaptophysin and Chromogranin A, combined with overwhelming positivity for Calcitonin and monoclonal CEA, is unequivocally pathognomonic for medullary thyroid carcinoma. The additional histological finding of amorphous amyloid deposits, which demonstrated apple-green birefringence on Congo Red staining, served as a classic, though not universally present, morphological corroboration.[15]

This case powerfully illustrates a critical, non-negotiable principle in modern oncologic pathology: in the workup of an atypical, destructive soft-tissue or bone mass, a comprehensive multi-lineage IHC panel (epithelial, sarcoma, neuroendocrine, melanocytic, and organ-specific markers) is not an academic luxury but a diagnostic necessity.[16] Furthermore, this systematic pathological investigation was corroborated by the parallel serological findings. The massively elevated serum calcitonin (>2000 pg/mL) and CEA (180 ng/mL) were, in themselves, definitive. This underscores the immense value of serum calcitonin as a "liquid biopsy." In an ideal diagnostic workflow for any patient presenting with an atypical bone or soft tissue metastasis, especially in the presence of a palpable thyroid nodule, these serum

markers should be drawn before an invasive procedure. In this case, the serology provided overwhelming evidence that was available even before the biopsy, transforming the pathological investigation from a "search" into a "confirmation."

Beyond the diagnostic challenge, this case presents a compelling biological question: how does a 30-year-old, clinically "indolent" thyroid nodule suddenly give rise to an explosive, exponentially-growing, sarcoma-like metastasis? This "two-speed" clinical history strongly suggests a process of clonal evolution within the primary tumor, culminating in the acquisition of a new, highly aggressive driver mutation. The primary 7.5 cm thyroid tumor should not be viewed as a monolith, but rather as a heterogeneous ecosystem of cancer cell populations that have evolved under selection pressures for three decades. It is highly plausible that the original tumor was a low-grade, indolent MTC, perhaps driven by a RAS mutation or a less potent RET mutation.[17] However, over time, due to inherent genomic instability, a single sub-clone within this primary tumor acquired a "second hit"—a catastrophic molecular event. This event was the somatic c.2753T>C (p.M918T) mutation in the RET proto-oncogene. The RET M918T substitution in exon 16 is not merely an activating mutation; it is the defining mutation of the most aggressive forms of MTC. It is the signature of the hereditary MEN2B syndrome and is found in 50-60% of advanced, high-risk sporadic MTCs, where it correlates strongly with high tumor burden, distant metastasis, and poor prognosis. This single amino acid change "locks" the RET kinase domain in a state of constitutive, ligand-independent, hyper-activation. This single molecular event unleashes a cascade of downstream signaling, primarily through the MAPK and PI3K/AKT pathways, which directly explains the three most prominent and aggressive features of this patient's metastatic lesion: (1) Proliferation and Invasion (Epithelial-Mesenchymal Transition - EMT): The hyper-activated MAPK and PI3K pathways converge to promote an aggressive cellular transformation known as EMT. They upregulate transcription factors (like SNAIL, ZEB1, and TWIST) that orchestrate a complex cellular reprogramming. This program represses E-cadherin, the "glue" that binds epithelial cells together, causing the cells to lose polarity and "let go" of their neighbors. Concurrently, it upregulates mesenchymal markers (like Vimentin and N-cadherin), transforming the static, cobblestone-like carcinoma cell into a migratory, invasive, spindle-shaped cell. This EMT process serves two functions in this case: it provides a mechanistic explanation for the "spindle cell" or "sarcomatoid" appearance seen on the biopsy, and it endows the cells with the invasive machinery required to escape the primary tumor, enter the bloodstream, and invade new tissues; (2) Hypervascularity and Growth (The "Angiogenic Switch"): The explosive 2-year growth and the "intense, avid enhancement" seen on MRI are not random. This is the direct result of a tumor-driven "angiogenic switch." The RET M918T mutation, via the PI3K/AKT pathway, leads to the stabilization of Hypoxia-Inducible Factor 1-alpha (HIF-1α), even in a normoxic environment. HIF-1α, in turn, potently upregulates the transcription of pro-angiogenic factors, most notably Vascular Endothelial Growth Factor (VEGF). The tumor cells flood their environment with VEGF, inducing a robust neovascularization that provides the massive blood supply necessary to fuel their exponential growth. This chaotic, rapidly-formed tumor vasculature is structurally abnormal and "leaky," which accounts for the heterogeneous enhancement and central necrosis seen on imaging. This process is identical to that seen in high-grade sarcomas and RCC, explaining the radiological mimicry; (3) Bone Destruction (The "Vicious Cycle"): The "seed and soil" hypothesis explains the localization to the shoulder; the red marrow of the scapula is a well-vascularized "soil" for circulating tumor "seeds." Once arrested in the scapular microcirculation, the MTC cells actively orchestrate the "gross lytic destruction" by initiating the "vicious cycle of bone metastasis." The MTC cells secrete osteoclast-activating factors, such as Receptor

Activator of Nuclear factor-κB Ligand (RANKL) and Parathyroid Hormone-related Peptide (PTHrP). These factors stimulate local osteoclasts to resorb bone, "drilling" lytic cavities to make space for the tumor. This bone resorption, in turn, releases a repository of growth factors (such as TGF-β) that were sequestered in the bone matrix. These newly-released growth factors then feedback on the tumor cells, stimulating them to proliferate more and secrete even more osteoclast-activating factors. This devastating positive feedback loop explains the "obliteration" of the scapula. Therefore, the 30-year indolent history followed by a 2-year aggressive metastatic course is likely the clinical manifestation of this profound molecular event: the emergence of a RET M918T-mutated sub-clone that was biologically programmed for invasion (EMT), hyper-angiogenesis (VEGF), and bone destruction (RANKL).[18]

Historically, management for metastatic MTC was an exercise in frustration. As a relatively slow-growing neuroendocrine tumor, MTC is profoundly resistant to conventional cytotoxic chemotherapy. Regimens like dacarbazine and doxorubicin offered poor objective response rates (10-20%), which were almost never durable, at the cost of significant toxicity. The first advancement came with the multi-kinase inhibitors (TKIs), Vandetanib and Cabozantinib. These drugs, which inhibit RET but also VEGFR, EGFR, and other kinases, were the first to show a clear progression-free survival benefit over placebo. However, this efficacy came at the cost of their "promiscuous" binding profile. These "dirty" TKIs are associated with significant off-target toxicities—including hypertension, diarrhea, rash, and QTc prolongation—that are often dose-limiting and lead to frequent dose reductions or discontinuations, thereby compromising long-term efficacy. The development of highly selective RET inhibitors—namely Selpercatinib (approved based on the LIBRETTO-001 trial) and Pralsetinib (approved based on the ARROW trial)—has completely revolutionized the treatment of this disease. These drugs are not "repurposed" TKIs; they are rationally designed, precision-engineered molecules built to fit exclusively into the ATP-binding pocket of the RET kinase. This "clean" target engagement has two profound benefits: (1) Profound Efficacy: Because off-target toxicity is minimal, the drugs can be dosed to achieve and maintain profound target inhibition, leading to the remarkable objective response rates of 70-80% seen in clinical trials; (2) Excellent Tolerability: The lack of off-target effects means patients can stay on therapy, often for years, allowing for durable, long-term disease control.[19]

This new therapeutic reality completely re-writes the management plan for this patient. In the pre-TKI era, a surgeon might have heroically but futilely attempted a high-morbidity "debulking" resection or forequarter amputation, knowing the patient had incurable M1 disease. In the modern era, this is inverted. The systemic therapy is the primary treatment; surgery's role becomes secondary, palliative, and strategic. The surgical plan formulated by the multidisciplinary team—controlling the primary tumor and regional disease (total thyroidectomy and neck dissection) while planning for neoadjuvant or palliative-intent systemic therapy before addressing the massive shoulder metastasis—is rooted in this new paradigm. The selective RET inhibitor will be the primary workhorse, very likely achieving significant cytoreduction of the shoulder mass.[20] This approach may render a future, less-morbid palliative surgery (such as a partial scapulectomy) safer and more effective for long-term local control and symptom palliation, or it may be so effective as to obviate the need for palliative surgery altogether. This case, therefore, perfectly encapsulates the modern oncologic paradigm: a sophisticated diagnostic workup, rooted in molecular understanding, leads directly to a targeted, effective, and tolerable therapy that transforms a rapidly fatal disease into a manageable chronic condition.

4. Conclusion

This report details an exceptionally rare presentation of sporadic medullary thyroid carcinoma, which masqueraded as a primary soft tissue sarcoma

of the shoulder, arising from a clinically indolent primary thyroid tumor of 30 years. This case underscores a critical diagnostic pitfall and emphasizes that MTC must be included in the differential diagnosis of any large, destructive, hypervascular bone and soft tissue mass, even in atypical locations. The definitive diagnosis was achieved not by a single test, but by a systematic, multidisciplinary approach that integrated clinical suspicion, serological biomarkers (Calcitonin/CEA), and a comprehensive immunohistochemical panel (thyroid-specific + MTC-specific) on the metastatic biopsy. Furthermore, it unlocked the most effective, modern management strategy by identifying the patient as a prime candidate for highly selective RET inhibitor therapy.

5. References

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