World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(CASE REPORT)

Check for updates

SPINDLE CELL SUBTYPE OF MEDULLARY THYROID CARCINOMA WITH SOMATIC RET M918T MUTATION: A CASE REPORT AND LITERATURE REVIEW

Corey Steinman [1], Sean Rockwell [2], Karen Sanabria [3], Phillip Pearson [4], Mohamed Aziz [5] and Jessica Jahoda [5, 6, *]

[1] American University of the Caribbean, AUC, St. Maarten.
[2] Ross University School of Medicine, Barbados.
[3] Ponce Health Sciences University (PHSU), Puerto Rico.
[4] Philadelphia College of Osteopathic Medicine, Georgia, Dept. of Biomedical Sciences, USA.
[5] Research Writing & Publication (RWP), LLC, NY, USA.
[6] Memorial Healthcare System, Pembroke Pines, FL, USA.
* Corresponding Author

ORCID Detail
Corey Steinman: https://orcid.org/ 0009-0002-5284-7337
Sean Rockwell: https://orcid.org/ 0009-0005-6131-7372
Karen Sanabria: https://orcid.org/0009-0005-5525-183X
Phillip Pearson: https://orcid.org/ 0000-0001-9945-152X
Mohamed Aziz: https://orcid.org/ 0000-0003-2397-0117
Jessica Jahoda: https://orcid.org/ 0009-0005-5196-3186

World Journal of Biology Pharmacy and Health Sciences, 2026, 27(02), 142–148

Publication history: Received on 12 June 2026; revised on 18 August 2026; accepted on 20 August 2026

Article DOI: https://doi.org/10.30574/wjbphs.2026.27.2.0434

Copyright © 2026 Author(s) retain the copyright of this article. This article is published under the terms of the Creative Commons Attribution License 4.0

ABSTRACT

The spindle cell subtype of medullary thyroid carcinoma (MTC) is an exceptionally rare morphologic pattern that can be mistaken cytologically and histologically for anaplastic thyroid carcinoma, sarcoma, melanoma, and other spindle cell lesions of the neck, creating a substantial diagnostic pitfall. We report a 72-year-old man who presented with an eight-month history of an enlarging, painless anterior neck mass accompanied by hoarseness, mild dysphagia, hot flushes, and unintentional weight loss. Examination revealed a firm 4 cm right thyroid nodule and a palpable left level VI lymph node; serum calcitonin exceeded 2000 pg/mL and carcinoembryonic antigen CEA) was 75 ng/mL. Fine-needle aspiration (FNA) demonstrated dispersed spindle-shaped cells within an amyloid-rich background, confirmed by Congo red birefringence and an immunohistochemical (IHC) profile positive for calcitonin, chromogranin A, synaptophysin, and CD56 and negative for thyroglobulin. Total thyroidectomy with comprehensive bilateral neck dissection confirmed bilateral spindle cell MTC with ten of thirty-two positive lymph nodes; molecular testing identified a somatic RET M918T mutation without RAS alteration, placing the patient in a high-risk prognostic category. Surveillance detected biochemical and structural relapse, with mediastinal and hepatic metastases at eighteen months, prompting initiation of a selective RET inhibitor. At two years, the patient remains on targeted therapy with stable disease and preserved

quality of life. This case underscores the importance of a systematic cytologic and IHC approach to spindle cell thyroid lesions and illustrates the evolving role of RET-directed therapy in advanced disease.

Keywords: Medullary thyroid carcinoma; Spindle cell morphology; Amyloid: Calcitonin; RET M918T mutation; Metastases

1 INTRODUCTION

MTC is a neuroendocrine malignancy arising from the calcitonin-secreting parafollicular C cells of the thyroid gland, accounting for a modest one to five percent of all thyroid cancers yet a disproportionate share, roughly thirteen percent, of thyroid-cancer-related mortality. [1] The overwhelming majority of cases, about seventy-five percent, are sporadic, while the remainder occur within hereditary multiple endocrine neoplasia type 2 syndromes driven by germline RET proto-oncogene mutations. [2]

The fifth edition of World Health Organization classification of endocrine and neuroendocrine tumors recognizes more than fourteen histological subtypes of MTC, of which the spindle cell subtype is among the rarest, with only a handful of cases described in the literature. [3] Its clinical presentation, a slowly enlarging neck mass often accompanied by hoarseness, dysphagia, or paraneoplastic flushing when calcitonin is markedly elevated, does not reliably distinguish it from other thyroid malignancies. [4]

Diagnostically, the spindle cell morphology is a well-recognized pitfall: it can closely mimic anaplastic thyroid carcinoma, spindle cell papillary carcinoma, primary thyroid sarcoma, melanoma, and fibroinflammatory conditions such as Riedel struma, and its amyloid-rich stroma may be mistaken for hyaline or collagenous material on cytology. [5,6] Reaching the correct diagnosis therefore depends on a deliberate combination of Congo red staining and an IHC panel confirming neuroendocrine and C-cell origin. [6]

Treatment centers on total thyroidectomy with appropriate neck dissection, while RET mutation status, particularly the aggressive M918T variant, increasingly informs both prognosis and, in advanced disease, eligibility for selective RET inhibitor therapy. [7,8] The case presented here, and the accompanying review, illustrate these diagnostic and therapeutic principles in a patient with an aggressive, RET M918T-positive spindle cell tumor.

2 CASE PRESENTATION

2.1 Clinical Presentation

A 72-year-old male presented with a progressively enlarging, painless anterior neck mass he had noticed for approximately eight months, associated with hoarseness and mild dysphagia over the preceding three months. He reported occasional hot flushes and a 5-pound weight loss. His past medical history was unremarkable for thyroid disease, and there was no family history of thyroid or endocrine malignancies. He had not sought prior medical attention for this swelling, and there was no history of neck irradiation. His presentation was prompted by worsening voice hoarseness and the noticeable growth of the mass, which he found cosmetically concerning.

2.2 Physical Examination and Diagnostic Workup

Physical examination revealed a firm, non-tender, 4 cm nodule in the right thyroid lobe that moved with swallowing, along with a palpable, firm, 2 cm left level VI lymph node. No cervical bruit or skin changes were noted. Laboratory studies showed markedly elevated serum calcitonin (>2000 pg/mL) and CEA levels (75 ng/mL). Thyroid function tests were within normal limits.

Neck ultrasonography identified a solid, hypoechoic, 4.2 cm nodule in the right lobe with microcalcifications and a suspicious 2.5 cm left paratracheal lymph node. A contrast-enhanced CT of the neck and chest confirmed the thyroid mass and left cervical lymphadenopathy, with no distant metastatic disease identified. The clinical and radiological differential diagnosis MTC, anaplastic thyroid carcinoma, and primary thyroid lymphoma, given the patient's age and the presence of cervical lymphadenopathy.

2.3 Multidisciplinary Tumor Board Discussion

The case was discussed at the multidisciplinary tumor board, focusing on elevated calcitonin and CEA levels that strongly suggested MTC. The radiographic findings of a solid, hypoechoic nodule with suspicious lymphadenopathy supported a diagnosis of locoregionally advanced disease. The team decided on a surgical management plan after diagnostic FNA cytology of the lesion. The plan included a total thyroidectomy with comprehensive bilateral central and

lateral neck dissection to achieve locoregional control and potential cure. Given suspicious lymphadenopathy, a thorough nodal clearance was deemed essential.

2.4 Special Studies, Surgical Treatment, and Pathology

Preoperative evaluation included an ultrasound-guided FNA of the thyroid nodule and an associated lymph node. Cytological examination of the aspirate revealed highly cellular smears predominantly composed of dispersed spindle-shaped cells characterized by scant cytoplasm and hyperchromatic, pleomorphic nuclei. The background exhibited amorphous, eosinophilic material consistent with amyloid deposition. IHC analysis of the cell block showed strong positivity for calcitonin, chromogranin A, synaptophysin, and CD56, with negative thyroglobulin. Congo red staining further confirmed the presence of amyloid, showing characteristic apple-green birefringence under polarized light. The FNA cytology was diagnostic of MTC with prominent spindle cell features.

The patient underwent total thyroidectomy and comprehensive bilateral neck dissection. Histopathological examination of the surgical specimen revealed irregularly arranged bundles of interlaced spindle-shaped cells. These cells had abundant cytoplasm and both short and long spindle nuclei, separated by a stroma containing fibrous tissue and extensive amyloid deposits (**Figure 1A, B, C, D).** A comprehensive differential diagnosis was conducted to distinguish the lesion from other thyroid and non-thyroid neoplasms, as summarized in Table (1)

Table 1: Differential diagnosis of Thyroid gland spindle cell lesions (References: 1, 6, 14, 17)

Differential Diagnosis	Distinguishing Features
Anaplastic Thyroid Carcinoma (spindle cell pattern)	Negative for calcitonin; high Ki-67 index; often presents with rhabdoid features.
Spindle Cell Metaplasia in Papillary Thyroid Carcinoma	Positive for keratin and TTF-1; negative for calcitonin.
Primary Thyroid Sarcoma	Extremely rare; typically, vimentin positive and cytokeratin negative. (extended IHC panel needed)
Spindle Cell Melanoma	Positive for S100, HMB-45, and Melan-A.
Riedel's Struma	Fibroinflammatory condition; lacks true neoplastic features.
Intrathyroidal Parathyroid Adenoma (spindle features)	Positive for PTH and GATA3.

The histomorphological findings, in conjunction with the IHC profile, confirmed the FNA diagnosis of bilateral MTC, spindle cell subtype, with extensive cervical lymph node metastasis (10 of 32 positive nodes). Molecular testing further identified a somatic RET M918T mutation and was negative for RAS mutations, thereby classifying the patient into a high-risk prognostic category.

2.5 Outcome and Follow-up

The immediate postoperative recovery was complicated by transient hypoparathyroidism, which resolved with calcium supplementation. He was initiated on a surveillance protocol with serum calcitonin and CEA measurements every three months.

At the 18-month follow-up, his calcitonin level had risen significantly to 800 pg/mL, and imaging revealed new, biopsy-confirmed metastatic disease in the mediastinum and a solitary liver lesion. The RET M918T-positive status made him a candidate for a selective RET inhibitor (selpercatinib or pralsetinib). He started on systemic targeted therapy, which was well-tolerated. At two years post-diagnosis, he continues this therapy with stable disease and an improved quality of life, with no further disease progression or significant drug-related adverse events.

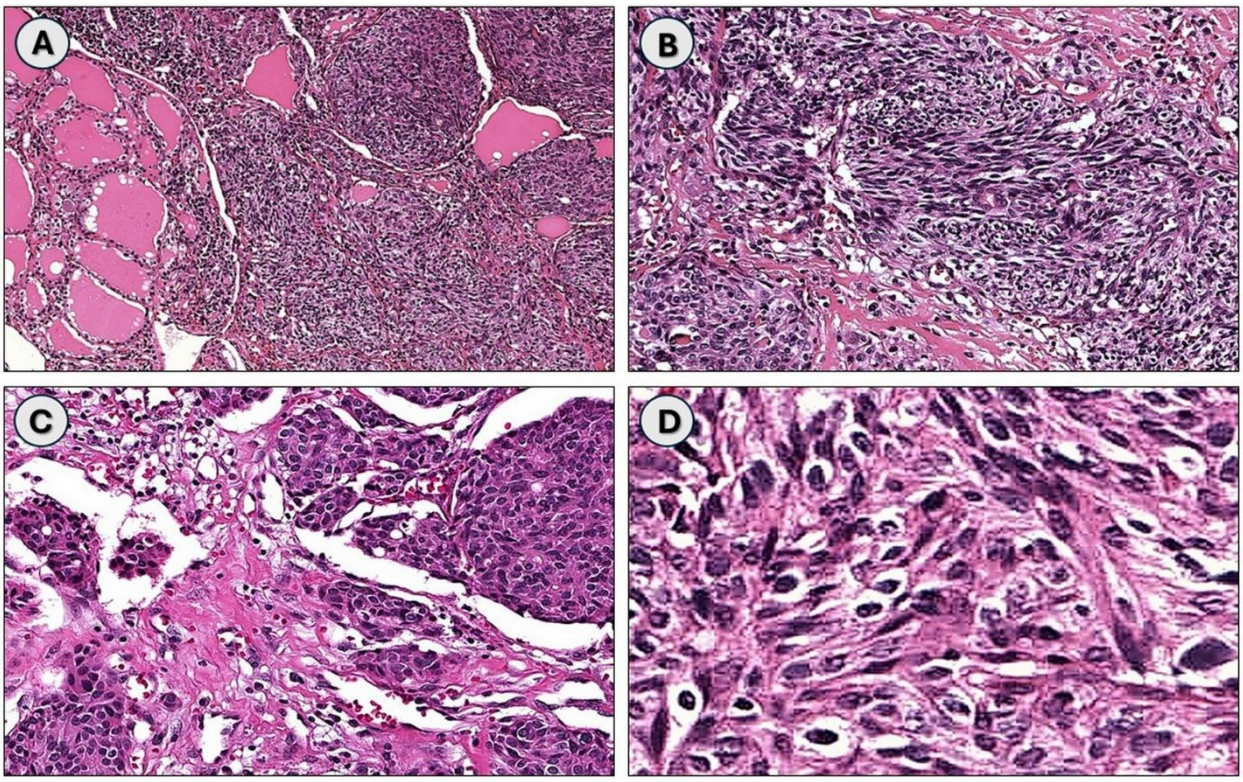

Figure 1: Microscopic features of spindle cell subtype of medullary thyroid carcinoma

- 1A**:** Low-power view showing infiltrating tumor into the thyroid parenchyma composed of solid sheets of spindle cells (H&E X20)
- 1B**:** Intermediate-power view showing irregularly arranged bundles of interlaced spindle-shaped cells (H&E X40)
- 1C**:** Intermediate-power view showing areas of amyloid deposits (H&E X40)
- 1D: High-power view featuring cells with abundant pink eosinophilic cytoplasm and both short and long spindle nuclei, separated by a stroma containing fibrous tissue and amyloid (H&E X60)

3 DISCUSSION

3.1 Background

Medullary thyroid carcinoma (MTC) is a neuroendocrine malignancy of the calcitonin-producing parafollicular C cells, distinct from the follicular-cell-derived cancers that make up the majority of thyroid malignancies. Estimates of its share of thyroid cancers vary modestly across sources, from roughly one to five percent in the most frequently cited reviews to as high as five to ten percent in other series. However, MTC consistently accounts for a disproportionate thirteen to thirteen-and-a-half percent of thyroid-cancer-related deaths, reflecting biology more aggressive than that of well-differentiated thyroid carcinoma. [1,3]

Approximately seventy-five percent of cases are sporadic, typically presented in the fifth to sixth decades of life, consistent with the 72-year-old patient described here. In comparison, the remaining twenty-five percent are hereditary, occurring within multiple endocrine neoplasia type 2A, type 2B, or familial MTC. These hereditary MTC each transmitted in an autosomal dominant pattern with near-complete penetrance for MTC and, depending on the syndrome, associated risk of pheochromocytoma, primary hyperparathyroidism, mucosal neuromas, and a marfanoid habitus. [2,9,10] Hereditary disease, particularly MEN2B, tends to present earlier, sometimes in infancy, which is why germline RET testing is recommended for every newly diagnosed patient with MTC. [4]

The fifth edition World Health Organization classification of endocrine and neuroendocrine tumors, published in 2022, reorganized thyroid tumor nomenclature, replacing the term variant with subtype for tumor subclasses and introducing a histologic grading system based on mitotic count, necrosis, and Ki-67 index; more than fourteen morphologic subtypes of MTC are now recognized, including papillary, follicular, giant cell, clear cell, and oncocytic patterns, alongside the exceedingly rare spindle cell subtype represented in this case. [11,3]

3.2 Pathogenesis, Pathophysiology

MTC arises from constitutive activation of the RET proto-oncogene, which encodes a transmembrane receptor tyrosine kinase; germline gain-of-function mutations underline the hereditary MEN2 syndromes. Somatic RET mutations are detectable in roughly forty-three to sixty-five percent of sporadic tumors, most commonly the M918T substitution in exon 16. [12,13] RET M918T is designated the highest-risk category within American Thyroid Association hereditary risk stratification and, in sporadic disease, correlates with larger tumor size at diagnosis, more advanced nodal and distant disease, and inferior prognosis. [7]

Constitutively active RET signaling drives unchecked C-cell proliferation and invasion. At the same time, the neoplastic cells retain their secretory phenotype, producing calcitonin and CEA and depositing calcitonin-derived amyloid within the tumor stroma, a hallmark present across all morphologic subtypes, including the spindle cell pattern, and confirmed by Congo red birefringence, as in this case. [14,5]

The precise mechanism of spindle morphologic transformation is not firmly established. However, a proposed proteomic classification of MTC into metabolic, basal, and mesenchymal molecular subtypes found that RET M918T-driven tumors are predominantly mesenchymal, offering a plausible molecular correlate for the spindle phenotype observed here. [15]

3.3 Comparative Analysis of Our Case with Existing Literature.

The present case can be usefully compared with the largest published series of spindle cell MTC, four patients described by Wang and Yang, whose IHC profile, calcitonin, chromogranin A, synaptophysin, CD56, and TTF-1 positive with thyroglobulin negative, closely mirrors that reported here; however, all four of their patients remained alive without recurrence at follow-up ranging from seven to eighty-four months, a considerably more indolent course than the bilateral, node-positive, and eventually metastatic disease observed in this patient. [3]

Singh and colleagues reported a 50-year-old man with a smaller, localized tumor cured by total thyroidectomy in the absence of metastatic disease, again illustrating a more favorable trajectory than the present case, which was RET M918T-positive and high-risk from the outset. [16]

Mondal and colleagues described a patient with a strikingly similar symptom profile, hoarseness, dyspnea, and dysphagia, together with nodal metastasis diagnosed through the same fine-needle aspiration, Congo red, and calcitonin pathway applied in this case. [5] Saini and colleagues emphasized that exclusively spindled aspirate smears raise a broad differential, including spindle epithelial tumor with thymus-like differentiation and spindle cell variants of anaplastic and papillary carcinoma, a pitfall this case similarly navigated through IHC and Congo red staining. [6]

Two older single-case reports, one describing a pseudoangiosarcomatous architectural pattern and another documenting hepatic metastasis from spindle cell MTC diagnosed by fine-needle aspiration, further illustrate the morphologic versatility of this subtype and its capacity to retain recognizable spindle morphology at distant metastatic sites, a consideration relevant to this patient's own hepatic and mediastinal relapse. [17,18]

4 WHAT HAVE WE LEARNED FROM THIS CASE?

This case offers several practical lessons for clinicians confronting a thyroid mass with atypical or ambiguous cytomorphology. Foremost, spindle cell cytology on thyroid fine-needle aspiration should never be presumed to represent a benign stromal, sarcomatous, or melanocytic process without excluding MTC, given the well-documented mimicry among these entities; glassy, amyloid-like background material should prompt Congo red staining and a directed IHC panel before a diagnosis of anaplastic carcinoma, sarcoma, or melanoma is rendered. [6,5]

Second, markedly elevated serum calcitonin and CEA, as seen in this patient, remain powerful diagnostic clues that should heighten suspicion for MTC even when cytology is morphologically unusual. Third, RET mutation testing should be performed routinely at diagnosis, since the M918T mutation identified here is an established marker of aggressive, high-risk disease that appropriately informed both the extent of surgery and, later, eligibility for targeted systemic therapy. Fourth, postoperative surveillance with serial calcitonin and CEA measurement proved essential in this patient, detecting biochemical relapse that preceded and predicted the subsequent identification of structural mediastinal and hepatic metastases.

Finally, this case reinforces the practice-changing shift toward selective RET inhibitor therapy, selpercatinib or pralsetinib, over older multikinase inhibitors in RET-altered advanced MTC, given the durable responses and favorable tolerability demonstrated in this patient and reported in the pivotal trials supporting these agents. [8,19] Taking

together, this case does not challenge existing knowledge so much as reaffirm, with a concrete and aggressive example, the importance of a systematic cytologic, IHC, and molecular diagnostic pathway for spindle cell thyroid lesions.

Abbreviations

- Medullary thyroid carcinoma (MTC);
- Fine-needle aspiration (FNA);
- Immunohistochemical (IHC)

5 CONCLUSION

This report describes a rare and diagnostically challenging spindle cell subtype of medullary thyroid carcinoma in a 72-year-old man whose markedly elevated calcitonin, amyloid-rich spindle cell cytology, and confirmatory immunohistochemical profile allowed a definitive preoperative diagnosis despite morphology that could easily have been mistaken for anaplastic carcinoma, sarcoma, or melanoma. The tumor's RET M918T mutation, extensive bilateral nodal metastasis, and subsequent mediastinal and hepatic relapse illustrate the aggressive end of the clinical spectrum reported for this subtype, in contrast to the more indolent courses described in most prior spindle cell MTC cases. The patient's sustained response to a selective RET inhibitor after relapse further demonstrates the practical value of routine RET testing in guiding systemic therapy for advanced disease. By documenting the complete diagnostic pathway, from FNA and Congo red staining through immunohistochemistry, molecular testing, and RET-directed treatment, this case adds a well-characterized, high-risk example to the limited body of literature on spindle cell MTC. It reinforces the systematic diagnostic approach needed whenever a thyroid gland spindle cell lesion is encountered.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgments

Special thanks to Jala El-Biali, and Andressa Balbi for their assistance in reviewing the final manuscript. Additionally, we appreciate the assistance of Grammarly's language editor and the Manus 1.6 program, which provided valuable writing support by identifying and correcting errors in grammar, spelling, punctuation, and writing style, ultimately enhancing the manuscript.

Disclosure of conflict of interest

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

This research does not include any studies involving 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.

Statement of informed consent

The patient was lost to follow-up, and all attempts to reach the patient were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

REFERENCES

[1] Santillan V R, Master S, Menon G, Burns B. Medullary Thyroid Cancer. StatPearls [Internet]. NCBI Bookshelf, updated 2024 Nov 10. https://www.ncbi.nlm.nih.gov/books/nbk459354

[2] Milićević S, Bergant D, Žagar T, Perić B. Crude annual incidence rate of medullary thyroid cancer and RET mutation frequency. Croatian Medical Journal. 2021 Apr 29;62(2):110-9.

[3] Wang YX, Yang SJ. Spindle cell variant of medullary thyroid carcinoma: a clinicopathologic study of four cases. Diagnostic Pathology. 2021 Nov 27;16:112..

[4] Gild ML, Clifton-Bligh RJ, Wirth LJ, Robinson BG. Medullary thyroid cancer: updates and challenges. Endocrine Reviews. 2023 Oct;44(5):934-46..

[5] Mondal SK, Nag DR, Bandyopadhyay R. Spindle cell variant of medullary carcinoma of thyroid with nodal metastasis: Cytodiagnosis and diagnostic dilemma. Thyroid Research and Practice. 2012;9(2):60-63.

[6] Saini T, Kundu R, Bhujade H. Extensive spindling in medullary thyroid carcinoma posing a diagnostic challenge: A case report. Diagnostic Cytopathology. 2022 Nov;50(11):E339-43.

[7] Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma. Thyroid. 2015;25(6):567-610.

[8] Wirth LJ, Sherman E, Robinson B, et al. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. New England Journal of Medicine. 2020;383:825-835.

[9] Zhang D, Liang N, Sun H, Frattini F, Sui C, Yang M, Wang H, Dionigi G. Critically evaluated key points on hereditary medullary thyroid carcinoma. Frontiers in Endocrinology. 2024 Jun 11;15:1412942.

[10] Tabatabaiefar MA, Moridnia A, Shariati L. Cancers of the endocrine system. Cancer Genetics and Psychotherapy. 2017 Sep 22:499-530.

[11] Jung CK, Bychkov A, Kakudo K. Update from the 2022 World Health Organization Classification of Thyroid Tumors: A Standardized Diagnostic Approach. Endocrinology and Metabolism (Korea). 2022;37(5):703-718.

[12] Larouche V, Akirov A, Thomas CM, Krzyzanowska MK, Ezzat S. A primer on the genetics of medullary thyroid cancer. Current Oncology. 2019 Dec 1;26(6):389.

[13] Kaliszewski K, Ludwig M, Ludwig B, Mikuła A, Greniuk M, Rudnicki J. Update on the diagnosis and management of medullary thyroid cancer: what has changed in recent years?. Cancers. 2022 Jul 27;14(15):3643.

[14] Wei S. Medullary thyroid carcinoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/thyroidmedullary.html. Accessed August 18th, 2026.

[15] Papachristos AJ, Serrao-Brown H, Gill AJ, Clifton-Bligh R, Sidhu SB. Medullary thyroid cancer: molecular drivers and immune cellular milieu of the tumour microenvironment—implications for systemic treatment. Cancers. 2024 Jun 22;16(13):2296..

[16] Singh S, Singh SK, Maurya G, Rashmi. Medullary thyroid carcinoma spindle cell variant: a rare case report. International Journal of Research in Medical Sciences. 2023;11(12):4555-4557.

[17] Laforga JB, Aranda FI. Pseudoangiosarcomatous features in medullary thyroid carcinoma spindle-cell variant. Report of a case studied by FNA and immunohistochemistry. Diagnostic Cytopathology. 2007;35(7):424-428.

[18] Ibarrola de Andres C, Castellano Megias VM, Ballestin Carcavilla C, Alberti Masgrau N, Perez-Barrios A. Hepatic metastases from the spindle cell variant of medullary thyroid carcinoma: report of a case with diagnosis by fine needle aspiration biopsy. Acta Cytologica. 2001;45(6):1022-1026.

[19] Subbiah V, Hu MI, Mansfield AS, Taylor MH, Schuler M, Zhu VW, Hadoux J, Curigliano G, Wirth L, Gainor JF, Alonso G. Pralsetinib in patients with advanced/metastatic rearranged during transfection (RET)-altered thyroid cancer: updated efficacy and safety data from the ARROW study. Thyroid®. 2024 Jan;34(1):26-40.