Early Online

The European Research Journal 2025 Case Report

DOI: https://doi.org/10.18621/eurj.1670211 *Medical Pathology*

Cytological misdiagnosis of high-grade medullary thyroid carcinoma with papillary-like nuclear features: A case report

Ali Mızrak

Department of Medical Pathology, Sultangazi Haseki Training and Research Hospital, İstanbul Türkiye

ABSTRACT

Medullary thyroid carcinoma is an uncommon form of thyroid cancer that arises from the parafollicular C cells. In this case report, a high-grade medullary thyroid carcinoma is discussed, which was initially diagnosed as papillary carcinoma due to the presence of papillary-like nuclear features in the cytological evaluation. A 65-year-old female presented to the ear, nose, and throat department with a palpable neck mass. Based on the cytological features of the fine needle aspiration (FNA), a diagnosis of 'malignant, papillary carcinoma', (Bethesda category 6) was made. After surgery, histological and immunohistochemical results led to a diagnosis of medullary thyroid carcinoma. Papillary carcinoma-like nuclear features may also be observed in medullary thyroid carcinoma and some cases could be mistakenly interpreted as papillary carcinoma in cytological examination.

Keywords: Cytology, intranuclear pseudo inclusions, medullary thyroid carcinoma, rearrangement during transfection (RET) gene mutation

Medullary thyroid carcinoma is an uncommon form of thyroid cancer that arises from the parafollicular C cells. Clinical findings, ultrasonographic features of the lesion, aspiration needle washout fluid, and serum biochemical markers can be helpful in establishing a diagnosis [1-3]. Immunohistochemical studies, combined with characteristic cytomorphological features observed in FNA samples, can be used to reach a definitive diagnosis [4-7]. However, medullary thyroid carcinoma may show various cytological and histological features that can be confused with many thyroid neoplasms [8, 9]. This case report discusses a high-grade medullary thyroid carcinoma with a rearrangement during transfection (RET) proto-oncogene mutation, initially misdiagnosed as papillary carcinoma in FNA cytology due to papillary-like nuclear features.

CASE PRESENTATION

A 65-year-old female presented to the ear, nose, and throat department with a palpable neck mass. Ultrasonographic examination revealed a solid mass lesion measuring 4·3 cm with irregular borders in the right lobe of the thyroid. A FNA was performed on the identified lesion. The samples were subsequently stained using Papanicolaou (PAP) and Giemsa stains. Although the cell block contained insufficient cells, the smears were cellular. Cytological examination re-

Received: April 4, 2025 **Accepted:** July 21, 2025 **Available Online:** July 22, 2025 **Published:** XX XX, 2025

How to cite this article: Mızrak A. Cytological misdiagnosis of high-grade medullary thyroid carcinoma with papillary-like nuclear features: A case report. Eur Res J. 2025. doi: 10.18621/eurj.1670211

Corresponding author: Ali Mızrak, MD., Phone: +90 212 453 20 00, E-mail: dralimizrak@gmail.com

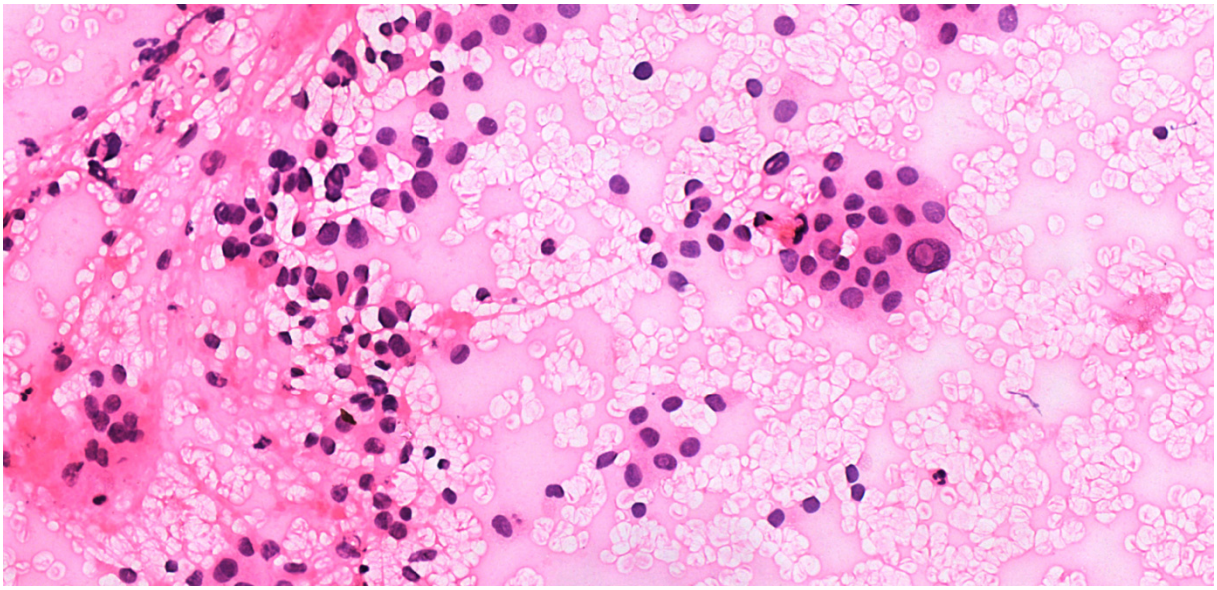

Fig. 1. **Cytological appearance of neoplastic cells (PAP, ×400).**

vealed nuclear enlargement, irregular borders, nuclear clearing, grooves, and intranuclear pseudo inclusions. The cytomorphological features resembled those of papillary thyroid carcinoma, leading to an initial misdiagnosis. The cytological diagnosis was reported as 'malignant, papillary thyroid carcinoma' based on the Bethesda classification (Fig. 1). The surgeon reviewed the radiological and cytological findings and decided to proceed with a total thyroidectomy. During surgery, it was noted that the lesion was adherent to the trachea, preventing the performance of a total thyroidectomy. The surgery was completed with a right thyroidectomy. Histological examination revealed a neoplastic lesion invading the surrounding muscle tissue. Acantholytic pseudopapillary structures were observed in the majority of the lesion. Other areas showed focal solid, follicular, and trabecular arrangements (Figs. 2 and 3). The cells exhibited nuclear clearing, grooves, and intranuclear pseudoinclusions. Numerous mitoses (15 in 2 mm^2) were observed under high magnification. Im-

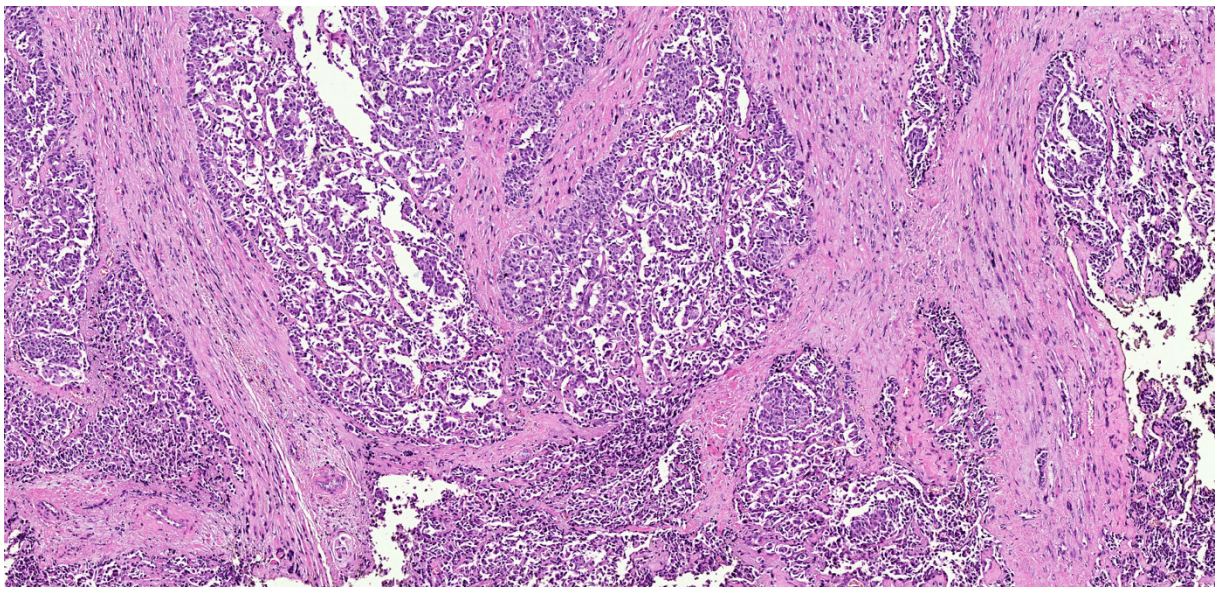

Fig. 2. **Thyroid medullary carcinoma (H&E, ×40).**

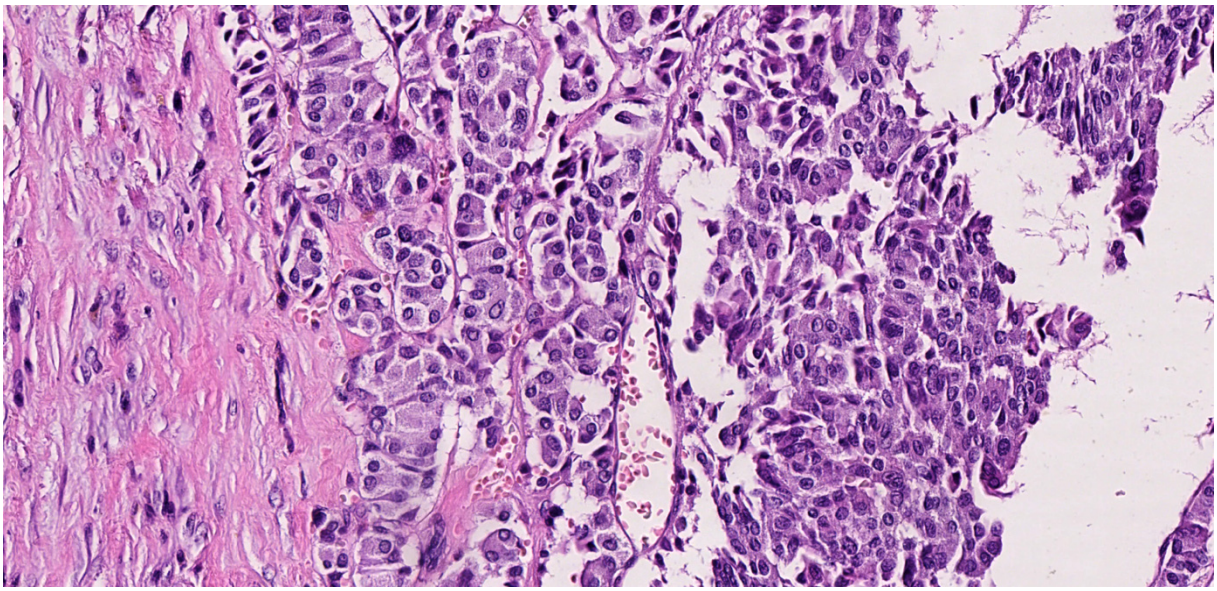

Fig. 3. Thyroid medullary carcinoma (H&E, ×400).

munohistochemical staining showed positivity for synaptophysin, chromogranin, thyroid transcription factor 1 (TTF-1), monoclonal carcinoembryonic antigen (m CEA), and calcitonin. The Ki-67 proliferation index was 50% in focal areas and averaged 20%. After surgery, histological and immunohistochemical results led to a diagnosis of medullary thyroid carcinoma. After the surgery, the patient's serum calcitonin level was found to be high (1395 ng/L). Molecular testing was conducted at the oncologist's request. Next-generation sequencing revealed a RET mutation in exon 16 (M918T) and exon 14 (V804L) of chromosome 10.

DISCUSSION

Medullary thyroid carcinoma represents a small proportion of all thyroid cancers. While not always achievable, preoperative diagnosis plays a crucial role in developing appropriate treatment strategies for patients. Clinicians or pathologists evaluating cytological samples should consider the possibility of medullary carcinoma, which could help reduce the risk of misdiagnosis. A major cause of misdiagnosis in pathological examination is the histological spectrum of thyroid medullary carcinoma, which can mimic nearly all other thyroid neoplasms [8, 9]. The presence of rare variants of thyroid medullary carcinoma adds another layer of complexity [10-12]. Azurophilic cytoplasmic granules, the presence of amyloid, plasmacytoid or spindle cells, and salt-and-pepper chromatin are the key cytologic features of medullary thyroid carcinoma. Papillary carcinoma-like nuclear features may also be observed. Cases showing all the features of ‘Indented membrane, and lobulation, ground-glass chromatin pattern and nuclear grooves' in cytological examination were accepted as ‘medullary thyroid carcinomas with papillary-like nuclear features’ by Yamao, and in the same study it was observed that some cases could be mistakenly interpreted as papillary carcinoma in cytological examination [13].

Numerous studies have explored the prognostic features of medullary thyroid carcinoma [14-17]. Recently, pathological grading has been advocated for medullary thyroid carcinoma. Different systems have been proposed for grading [18-20]. Mitosis, necrosis, and Ki-67 proliferation index are the key parameters used in these grading systems. In recent publications, two-grade (high grade-low grade) and three-grade (low-intermediate-high grade) classification systems have been suggested for grading thyroid medullary carcinoma. Based on these classification systems, our case falls into the high-grade category, with a Ki-67 proliferation index of 20% and 15 mitoses per 2 mm². The occurrence of sporadic medullary thyroid carcinoma is linked to somatic mutations in the RET gene [21]. In our case, two mutations were identified in the RET gene: exon 16 (M918T) and exon 14 (V804L).

CONCLUSION

Although not always indicative of high-grade malignancy, thyroid medullary carcinoma exhibiting papillary-like nuclear features should be considered in the differential diagnosis of cytological samples. Immunohistochemical studies can be conducted on both cell blocks and smears, yielding reliable results.

Ethical Statement

Since this is a case report presentation, no ethics committee approval was required; however, informed consent of writing and publication was obtained from the patient prior to the preparation of the manuscript.

Patient' Consent

Patient was informed about the purpose of the case report, and written informed consent was obtained from the patient for publication of this case and any accompanying pictures or data.

Authors' Contribution

Study Conception: AMzk; Study Design: AMzk; Supervision: AMzk; Funding: N/A; Materials: AMzk; Data Collection and/or Processing: AMzk; Statistical Analysis and/or Data Interpretation: AMzk; Literature Review: AMzk; Manuscript Preparation: AMzk; and Critical Review: AMzk.

Conflict of interest

The author(s) disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author(s) disclosed that they did not receive any grant during the conduction or writing of this study.

Generative Artificial Intelligence Statement

The author(s) declare that no artificial intelligence-based tools or applications were used. The all content of the study was produced by the author(s) in accordance with scientific research methods and academic ethical principles.

Editor's note

All statements made in this article are solely those of the authors and do not represent the views of their affiliates or the publisher, editors, or reviewers. Any claims made by any product or manufacturer that may be evaluated in this article are not guaranteed or endorsed by the publisher.

REFERENCES

1. Trimboli P, Crescenzi A. Diagnosing medullary thyroid carcinoma is facilitated by measuring calcitonin in FNA washout fluids: Alea iacta est. Cancer Cytopathol. 2024;132(3):139. doi: 10.1002/cncy.22797.
2. Ogmen BE, Ince N, Aksoy Altınboga A, et al. An old friend, a new insight: Calcitonin measurement in serum and aspiration needle washout fluids significantly increases the early and accurate detection of medullary thyroid cancer. Cancer Cytopathol. 2024 Mar;132(3):161-168. doi: 10.1002/cncy.22779.
3. Liu S, Zhao H, Li X. Serum Biochemical Markers for Medullary Thyroid Carcinoma: An Update. Cancer Manag Res. 2024;16:299-310. doi: 10.2147/CMAR.S440477.
4. Nikas IP, Kazamias G, Vrontaki M, Rapti AS, Mastorakis E. Medullary thyroid carcinoma diagnosed with liquid-based cytology and immunocytochemistry. J Immunoassay Immunochem. 2022;43(5):502-515. doi: 10.1080/15321819.2022.2070025.
5. Liu CY, Chen CC, Bychkov A, et al. Constitutive Cytomorphologic Features of Medullary Thyroid Carcinoma Using Different Staining Methods. Diagnostics (Basel). 2021;11(8):1396. doi: 10.3390/diagnostics11081396.
6. Ahmed M, Abi-Raad R, Fu L, Holt EH, Adeniran AJ, Cai G. Performing Calcitonin Immunocytochemistry on an Additional ThinPrep Slide in Fine-Needle Aspiration Diagnosis of Medullary Thyroid Carcinoma. Am J Clin Pathol. 2022;157(3):426-433. doi: 10.1093/ajcp/aqab141.
7. Trimboli P, Treglia G, Guidobaldi L, et al. Detection rate of FNA cytology in medullary thyroid carcinoma: a meta-analysis. Clin Endocrinol (Oxf). 2015;82(2):280-285. doi: 10.1111/cen.12563.
8. Kang M, Kim NR, Seok JY. Non-papillary thyroid carcinoma diagnoses in The Bethesda System for Reporting Thyroid Cytopathology categories V and VI: An institutional experience. Ann Diagn Pathol. 2024;71:152263. doi: 10.1016/j.anndiagpath.2023.152263.
9. Agarwal C, Raychaudhuri S, Batra A, Pujani M, Dhingra S. Medullary carcinoma of thyroid mimicking Hurthle cell neoplasm on cytology: a diagnostic dilemma. Diagn Cytopathol. 2019;47(9):943-947. doi: 10.1002/dc.24220.
10. Kaushal S, Iyer VK, Mathur SR, Ray R. Fine needle aspiration cytology of medullary carcinoma of the thyroid with a focus on rare variants: a review of 78 cases. Cytopathology. 2011;22(2):95-105. doi: 10.1111/j.1365-2303.2010.00747.x.
11. Schreiner AM, Yang GC. Medullary thyroid carcinoma presenting as rectangular cell type on fine-needle aspiration. Diagn Cytopathol. 2009;37(3):213-216. doi: 10.1002/dc.21041.
12. Trivedi D, George L. An Aggressive Form of Medullary Thyroid Carcinoma-Melanocytic Subtype: A Case Report. Cureus. 2023;15(12):e50310. doi: 10.7759/cureus.50310.

13. Yamao N, Hirokawa M, Suzuki A, et al. High-grade medullary thyroid carcinoma with papillary-like nuclear features: A report of five cases. Diagn Cytopathol. 2024;52(1):58-64. doi: 10.1002/dc.25243.
14. Aksoy YA, Xu B, Viswanathan K, et al. Novel prognostic nomogram for predicting recurrence-free survival in medullary thyroid carcinoma. Histopathology. 2024;84(6):947-959. doi: 10.1111/his.15141.
15. Wang Z, Fan X, Zha X, et al. A Proposed Modified Staging System for Medullary Thyroid Cancer: A SEER Analysis With Multicenter Validation. Oncologist. 2024;29(1):e59-e67. doi: 10.1093/oncolo/oyad165.
16. Najdawi F, Ahmadi S, Capelletti M, Dong F, Chau NG, Barletta JA. Evaluation of grade in a genotyped cohort of sporadic medullary thyroid carcinomas. Histopathology. 2021;79(3):427-436. doi: 10.1111/his.14370.
17. Toraih E, Hussein M, Anker A, et al. Survival Outcomes of Medullary Thyroid Cancer With and Without Amyloid Deposition. Endocr Pract. 2024;30(4):311-318. doi: 10.1016/j.eprac.2024.01.001.
18. Fuchs TL, Nassour AJ, Glover A, et al. A Proposed Grading Scheme for Medullary Thyroid Carcinoma Based on Proliferative Activity (Ki-67 and Mitotic Count) and Coagulative Necrosis. Am J Surg Pathol. 2020;44(10):1419-1428. doi: 10.1097/PAS.0000000000001505.
19. Alzumaili B, Xu B, Spanheimer PM, et al. Grading of medullary thyroid carcinoma on the basis of tumor necrosis and high mitotic rate is an independent predictor of poor outcome. Mod Pathol. 2020;33(9):1690-1701. doi: 10.1038/s41379-020-0532-1.
20. Xu B, Fuchs TL, Ahmadi S, et al. International Medullary Thyroid Carcinoma Grading System: A Validated Grading System for Medullary Thyroid Carcinoma. J Clin Oncol. 2022;40(1):96-104. doi: 10.1200/JCO.21.01329.
21. Dvoráková S, Václavíková E, Sýkorová V, et al. New multiple somatic mutations in the RET proto-oncogene associated with a sporadic medullary thyroid carcinoma. Thyroid. 2006;16(3):311-316. doi: 10.1089/thy.2006.16.311.