

(CASE REPORT)



ANAPLASTIC THYROID CARCINOMA 10 YEARS FOLLOWING PAPILLARY THYROID CARCINOMA: A CASE REPORT OF MIXED HISTOMORPHOLOGY AND DIAGNOSTIC CHALLENGE

Grace Durham ¹, Cindy Almaraz ², Corey Steinman ³, Phillip Pearson ⁴, Mohamed Aziz ⁶ and Jessica Jahoda ^{5, 6, *}

¹ University of South Florida, Tampa, FL, USA.

² Ross University School of Medicine, Barbados.

³ American University of the Caribbean, AUC, St. Maarten.

⁴ Philadelphia College of Osteopathic Medicine, Georgia, Dept. of Biomedical Sciences, USA.

⁵ Memorial Healthcare System, Pembroke Pines, FL, USA.

⁶ Research Writing & Publication (RWP), LLC, NY, USA.

* Corresponding Author

ORCID Details

Grace Durham: <https://orcid.org/0009-0009-2026-041X>

Cindy Almaraz: <https://orcid.org/0009-0007-7759-968X>

Corey Steinman: <https://orcid.org/0009-0002-5284-7337>

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), 040–046

Publication history: Received on 29 June 2026; revised on 09 August 2026; accepted on 11 August 2026

Article DOI: <https://doi.org/10.30574/wjbphs.2026.27.2.0424>

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

Anaplastic thyroid carcinoma (ATC) is a rare, highly aggressive thyroid malignancy associated with rapid progression, diagnostic complexity, and poor prognosis, particularly true when arising through dedifferentiation of pre-existing papillary thyroid carcinoma (PTC).

We present the case of a 63-year-old female with a history of papillary thyroid carcinoma (PTC) previously treated with total thyroidectomy and radioactive iodine ablation 10 years prior. She presented with a rapidly enlarging anterior neck mass, progressive dysphagia, hoarseness, and intermittent stridor. Imaging revealed a locally invasive necrotic mass with intense hypermetabolic activity. Histopathological examination demonstrated mixed histomorphologic features, including spindle cell, squamous, and clear cell differentiation, while subsequent molecular analysis identified BRAF V600E and TERT promoter mutations. Together, these findings supported the diagnosis of anaplastic thyroid carcinoma. Guided by a multidisciplinary tumor board, the patient underwent tracheostomy, palliative radiotherapy, and targeted therapy with dabrafenib and trametinib. However, despite initial stabilization, the patient died of progressive disease nine months after diagnosis.

This case illustrates how a decade-long latency, mixed histomorphology, and a high-risk molecular profile can complicate the recognition of anaplastic transformation. It underscores the diagnostic and therapeutic pathway required for optimal management.

Keywords: Anaplastic thyroid carcinoma; Papillary thyroid carcinoma; Undifferentiated; Dedifferentiation; Aggressive; Mixed histomorphology; BRAF V600E mutant protein

1 INTRODUCTION

Anaplastic thyroid carcinoma (ATC) is an undifferentiated malignancy of follicular cell origin and the most lethal of all thyroid cancers, with every case classified as stage IV at diagnosis regardless of tumor size or extent. [1] It arises either de novo or through dedifferentiation of a pre-existing differentiated thyroid carcinoma, most often papillary, a process driven by the sequential accumulation of genetic alterations superimposed on an early driver mutation such as BRAF V600E. [2,3] Because ATC frequently presents with rapid local invasion and airway compromise, timely recognition and multidisciplinary coordination are essential to any chance of disease control. [4]

This case merits reporting for several converging reasons. The patient's anaplastic carcinoma emerged a full decade after definitive treatment of PTC, a long enough latency that anaplastic transformation was not the leading clinical suspicion. The tumor's mixed morphology, combining spindle cell, squamous, and clear cell elements, produced a broad differential diagnosis extending to lymphoma and metastatic renal cell carcinoma. Confirmation required an immunohistochemical (IHC) and molecular workup culminating in a BRAF V600E mutation with a concurrent TERT promoter mutation, a combination associated with particularly aggressive behavior. [3] The subsequent use of dabrafenib and trametinib places this case within a still-limited body of real-world experience with targeted therapy in this disease.

2 CASE PRESENTATION

2.1 Clinical Presentation

A 63-year-old female with a history of PTC, previously managed with total thyroidectomy and radioactive iodine ablation ten years prior, presented with a rapidly enlarging anterior neck mass that had progressed over six weeks, accompanied by progressive dysphagia, hoarseness, and intermittent stridor. She sought medical attention due to worsening dyspnea and significant pain in the neck region. The patient reported no prior neck radiation exposure and had a family history negative for thyroid malignancies.

2.2 Physical Examination, Labs, Imaging, and Differential Diagnosis

Physical examination revealed a large, firm, and fixed mass in the left anterior neck measuring approximately 7 cm, with overlying skin erythema and evidence of tracheal deviation. Left vocal cord paralysis was confirmed via laryngoscopy, and palpable cervical lymphadenopathy was noted in the left levels III and IV. Thyroid function tests were within normal limits.

A contrast-enhanced CT scan of the neck and chest demonstrated a 7.5 cm heterogeneous, necrotic mass invading the trachea and esophagus, along with multiple bilateral pulmonary nodules and mediastinal lymphadenopathy, indicative of distant metastatic disease. A PET-CT scan revealed intensely hypermetabolic activity in the primary tumor, cervical nodes, and pulmonary lesions. The clinical and radiological differential diagnosis included anaplastic transformation of the prior papillary carcinoma, primary thyroid lymphoma, or metastatic disease to the thyroid, such as renal cell carcinoma.

2.3 Multidisciplinary Tumor Board Discussion and Management Plan

The multidisciplinary tumor board, comprising endocrinologists, surgeons, medical and radiation oncologists, and pathologists, reviewed the case. The central discussion focused on the patient's stage IVC disease, rendering her unresectable with curative intent. The pathologist explained that even with prior total thyroidectomy, anaplastic thyroid carcinoma can develop from microscopic remnants of the original papillary thyroid cancer or microscopic normal thyroid tissue left behind during surgery, or from dormant metastatic cancer cells in nearby lymph nodes that underwent a rare genetic transformation into an aggressive, undifferentiated state.

The team emphasized the critical need for expedited molecular testing to identify actionable mutations, particularly BRAF V600E, which is present in up to 45% of anaplastic thyroid carcinomas, and for early integration of palliative care.

to address goals of care. The consensus was to initiate systemic therapy with a BRAF/MEK inhibitor combination following confirmation of a BRAF V600E mutation. It demonstrated efficacy in improving outcomes for this aggressive disease. A tracheostomy was recommended to secure the airway, and palliative radiotherapy was considered for local symptom control.

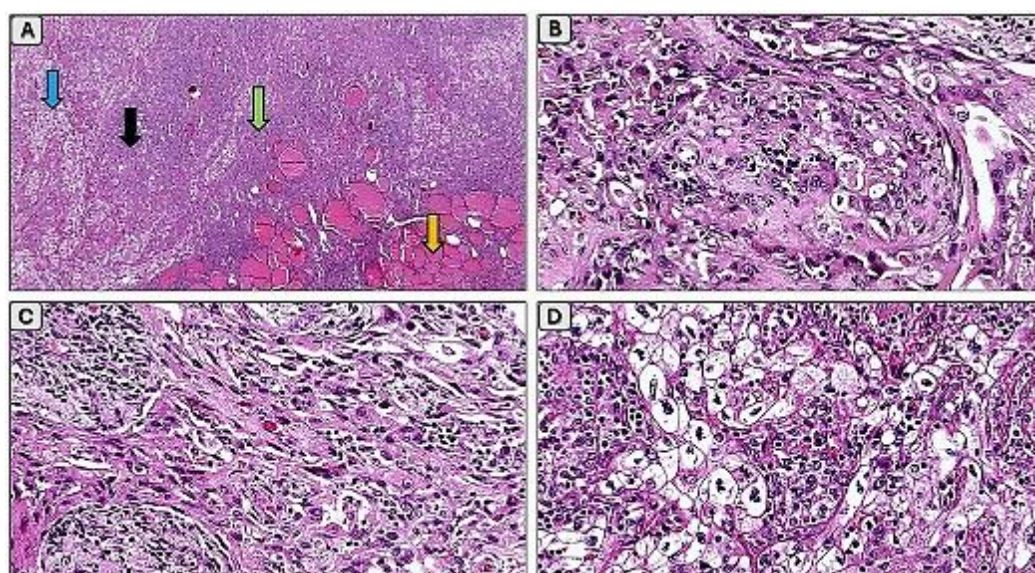
2.4 Special Studies, Pathology, and Immunohistochemistry

A core needle biopsy of the neck mass was performed. Histopathological examination revealed a highly pleomorphic tumor with a mixed morphology comprising areas of malignant spindle cells, squamous differentiation, and nests of cells with clear cytoplasm. IHC demonstrated negative TTF-1 and thyroglobulin reaction, confirming dedifferentiation, while PAX-8 was retained in approximately half of the tumor cells, supporting a thyroid origin.

The tumor showed diffuse, strong positivity for BRAF V600E mutant protein, and a high Ki-67 proliferative index of 70% was noted, consistent with its aggressive behavior. Next-generation sequencing confirmed the BRAF V600E mutation and identified a concurrent TERT promoter mutation, further correlating with a poor prognosis and high metastatic potential.

2.5 Treatment, Outcome, and Follow-up

The patient initiated the combination targeted therapy with dabrafenib and trametinib and received palliative radiotherapy to the neck for local symptom management. Despite initial stabilization of her symptoms, she experienced progressive disease with worsening pulmonary metastases and developed significant treatment-related fatigue. After a goals-of-care discussion, the patient opted to transition to hospice care. The patient expired nine months after her anaplastic carcinoma diagnosis.



1A: Low-power view showing mixed histologic features with clear cell features (blue arrow), squamous cell features (black arrow), and spindle cell features (green arrow). Yellow arrow points to non-neoplastic thyroid tissue (H&E X20); 1B: High-power view showing squamous features (H&E X40); 1C: High-power view showing spindle cell features (H&E X60); 1D: High-power view showing clear cell features

Figure 1: Microscopic features of thyroid anaplastic carcinoma with mixed histomorphologic features

3 DISCUSSION

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

ATC was formally distinguished from other undifferentiated thyroid malignancies decades ago, and the World Health Organization (WHO) has consistently favored the term "anaplastic" over "undifferentiated" in its classification of endocrine tumors. [1,5] ATC accounts for only 1% to 4% of thyroid cancers yet contributes disproportionately, roughly 14% to 39%, to thyroid cancer mortality. [1] It occurs predominantly in patients in their seventh and eighth decades of life, with a female predominance reported across large series, at ratios of roughly 1.3 to 3.7 to 1. [1, 5] The dominant risk factor is a pre-existing or coexisting differentiated thyroid carcinoma: large surgical series find papillary, follicular, or Hürthle cell carcinoma admixed with or antecedent to ATC in more than half of cases, alongside a long-standing goiter in a substantial minority of patients. [1,6] Prior external radiation exposure is a recognized but less common contributor.

The WHO's fifth edition classification of endocrine and neuroendocrine tumors retains ATC as an undifferentiated, follicular-cell-derived carcinoma and now formally incorporates primary squamous cell carcinoma of the thyroid as a distinct ATC subtype, reflecting molecular and behavioral overlap between these historically separate diagnoses [6]. Both terms, anaplastic and undifferentiated, are used by the WHO, but they serve different naming roles: "Anaplastic thyroid carcinoma" is the official diagnostic name (the primary term), while "undifferentiated" is used as the descriptive term to define its biological behavior and category. The 5th edition WHO blue book explicitly indexes it as "Anaplastic (undifferentiated) carcinoma". [7,8]

Dedifferentiation from papillary thyroid carcinoma proceeds through progressive loss of thyroid-specific markers, such as thyroglobulin and TTF-1, and accumulation of late-event mutations in TP53, the TERT promoter, and the PI3K pathway atop an early BRAF or RAS driver. [3,6]

3.2 Pathogenesis, Pathophysiology

ATC is an undifferentiated, follicular-cell-derived thyroid cancer. It usually results from stepwise dedifferentiation of an existing papillary or follicular thyroid carcinoma, although it can arise *de novo*. Accumulated genetic alterations lead to loss of thyroid-cell identity, explosive local growth, invasion, and early metastasis. [9] ATC derives from thyroid follicular epithelial cells. In many tumors, a differentiated thyroid carcinoma component is present, and both components share an early driver mutation, supporting transformation from differentiated thyroid cancer (DTC) to ATC. [9]

Early oncogenic drivers, such as BRAF V600E or RAS, activate mitogenic signaling but are not sufficient on their own to cause ATC. Additional "second hits" create an anaplastic phenotype. [10] Common changes include TP53 inactivation (loss of DNA-damage checkpoint/apoptotic control), TERT promoter mutations (telomerase reactivation and cellular immortality), and abnormalities in PIK3CA, PTEN, CDKN2A/CDKN2B, and CCNE1. These promote genomic instability, PI3K–AKT signaling, loss of cell-cycle control, and unchecked proliferation. [6,10] MAPK signaling (RAS–RAF–MEK–ERK) and PI3K–AKT–mTOR signaling are frequently activated. Altered adhesion, epithelial–mesenchymal transition–like behavior, angiogenesis, and DNA-repair defects further enable invasion and treatment resistance. [9, 10]

The malignant cells lose normal follicular functions, particularly thyroglobulin synthesis and iodine uptake, so ATC generally does not respond to radioactive iodine therapy. [9, 11] Histologically, it consists of markedly pleomorphic spindle cells, giant cells, and/or squamous cells, with extremely high mitotic activity, tumor necrosis, and frequent vascular invasion. [9, 13] Its aggressive proliferation and invasive capacity cause direct extension into neck structures, trachea, larynx, esophagus, recurrent laryngeal nerves, muscle, and vessels. This produces a rapidly enlarging hard neck mass, dyspnea/stridor, dysphagia, hoarseness, pain, and sometimes life-threatening airway compromise. [9,12]

Lymphovascular invasion and biologically aggressive clones permit early regional nodal and distant metastases, commonly to the lungs, bones, and brain. [13] ATC's lethality is driven primarily by local airway/neck invasion and metastatic disease, rather than by excess thyroid hormone production. [9]

3.3 Comparative Analysis of Our Case with Existing Literature.

This case aligns closely with and, in some respects, extends the published literature on anaplastic transformation arising from papillary thyroid carcinoma. Park et al. reported an anaplastic transformation of PTC, confirmed by BRAF analysis, in a younger patient, establishing that the same BRAF-driven dedifferentiation pathway operates outside the typical elderly demographic. However, our patient's presentation at 63, with a decade-long latency, is more representative of the usual clinical course. [14]

Song et al. described papillary thyroid carcinoma and its anaplastic transformation coexisting within a single cervical lymph node metastasis, a juxtaposition of differentiated and undifferentiated components analogous to the mixed lineage evident on this patient's biopsy. [15]

Most directly comparable is the report by Zhang et al. of a tumor combining papillary carcinoma, a squamous cell carcinoma subtype of anaplastic thyroid carcinoma, and poorly differentiated carcinoma within one specimen, which mirrors the spindle cell, squamous, and clear cell heterogeneity described here and reinforces the WHO's formal recognition of squamous differentiation as an ATC subtype rather than a separate entity. [7,16]

At the population level, Xu et al.'s series of 360 cases found BRAF mutations concentrated in tumors with an antecedent or coexisting papillary component, consistent with this patient's history, while Shi et al. and Pozdeyev et al. independently linked concurrent BRAF V600E and TERT promoter mutations to older age and greater distant metastatic burden, both features borne out in this patient's pulmonary dissemination. [3,6,17]

Her nine-month survival on dabrafenib and trametinib falls within, though toward the lower end of, outcomes reported in the ROAR basket trial, underscoring that molecularly matched therapy extends but does not overturn the disease's aggressive trajectory. [18]

4 WHAT HAVE WE LEARNED FROM THIS CASE?

This case reinforces that a remote history of differentiated thyroid carcinoma does not close the door to anaplastic transformation, even a decade after apparent cure. Rapid neck mass growth, new compressive symptoms, or vocal cord paralysis in such a patient should prompt urgent tissue diagnosis rather than reassurance based on prior benign surveillance.

The mixed spindle cell, squamous, and clear cell morphology encountered here shows why thyroid-specific markers alone are insufficient for diagnosis; PAX-8 and BRAF V600E IHC, paired with next-generation sequencing, were necessary to secure a thyroid origin and exclude lymphoma and metastatic disease. The co-occurrence of BRAF V600E with a TERT promoter mutation should be treated as a signal of aggressive biology that warrants early, frank goals-of-care discussion alongside initiation of targeted therapy. Finally, the case affirms that dabrafenib and trametinib provide meaningful but time-limited disease control, and that airway security and palliative radiotherapy remain integral to management in addition to molecular findings.

Abbreviations

- Anaplastic thyroid carcinoma (ATC);
- Papillary thyroid carcinoma (PTC);
- Immunohistochemical (IHC)

5 CONCLUSION

This case adds a well-documented example of mixed-morphology anaplastic thyroid carcinoma arising a decade after treated papillary thyroid carcinoma, combining a diagnostically challenging histologic picture with a high-risk BRAF V600E and TERT promoter co-mutation. It demonstrates, in a real-world patient with extensive unresectable metastatic disease, the expected magnitude of benefit from dabrafenib plus trametinib relative to historical outcomes.

We present it to reinforce two points for the clinical community: anaplastic transformation must remain on the differential for any patient with a distant history of differentiated thyroid cancer who develops a rapidly growing neck mass. Molecular characterization should be pursued urgently, since it defines both the diagnosis and the only therapy shown to alter this disease, which otherwise has a uniformly poor course.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgments

Special thanks to Andressa Balbi, MD, 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 work did not involve any studies on human or animal subjects performed by the authors. It was a retrospective review of archival pathology material collected during routine clinical care, and all data were fully de-identified before analysis.

Statement of informed consent

The patient expired, and all attempts to reach the family members 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] Abe I, Lam AK. Anaplastic thyroid carcinoma: Updates on WHO classification, clinicopathological features and staging. *Histology and histopathology*. 2020.
- [2] Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark Jr TJ, Di Cristofano A, Foote R, Giordano T, Kasperbauer J, Newbold K. 2021 American thyroid association guidelines for management of patients with anaplastic thyroid cancer: American thyroid association anaplastic thyroid cancer guidelines task force. *Thyroid*. 2021 Mar;31(3):337-86.
- [3] Pozdeyev N, Gay LM, Sokol ES, Hartmaier R, Deaver KE, Davis S, French JD, Borre PV, LaBarbera DV, Tan AC, Schweppe RE. Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. *Clinical Cancer Research*. 2018 Jul 1;24(13):3059-68.
- [4] Smallridge RC, Ain KB, Asa SL, Bible KC, Brierley JD, Burman KD, Kebebew E, Lee NY, Nikiforov YE, Rosenthal MS, Shah MH. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2012 Nov;22(11):1104-39.
- [5] Jung CK, Bychkov A, Kakudo K. Update from the 2022 World Health Organization classification of thyroid tumors: a standardized diagnostic approach. *Endocrinology and Metabolism*. 2022 Oct 4;37(5):703-18.
- [6] Xu B, Fuchs T, Dogan S, Landa I, Katabi N, Fagin JA, Tuttle RM, Sherman E, Gill AJ, Ghossein R. Dissecting anaplastic thyroid carcinoma: a comprehensive clinical, histologic, immunophenotypic, and molecular study of 360 cases. *Thyroid*. 2020 Oct;30(10):1505-17.
- [7] Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G, Mete O. Overview of the 2022 WHO classification of thyroid neoplasms. *Endocrine pathology*. 2022 Mar;33(1):27-63.
- [8] Wirth P. WHO classification. PathologyOutlines.com website. <https://www.pathologyoutlines.com/topic/thyroidwho.html>. Accessed August 8th, 2026.
- [9] Alhejaily AG, Alhuzim O, Alwelaie Y. Anaplastic thyroid cancer: Pathogenesis, prognostic factors and genetic landscape (Review). *Mol Clin Oncol*. 2023 Nov 2;19(6):99.
- [10] Smallridge, R. C., Marlow, L. A., & Copland, J. A. (2008). Anaplastic Thyroid Cancer: Molecular Pathogenesis and Emerging Therapies (Review) 2.
- [11] Rao SN, Smallridge RC. Anaplastic thyroid cancer: An update. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2023 Jan 1;37(1):101678..
- [12] Oishi N, Kondo T, Ebina A, Sato Y, Akaishi J, Hino R, Yamamoto N, Mochizuki K, Nakazawa T, Yokomichi H, et al: Molecular alterations of coexisting thyroid papillary carcinoma and anaplastic carcinoma: Identification of TERT mutation as an independent risk factor for transformation
- [13] Khatami F, Tavangar SM. A review of driver genetic alterations in thyroid cancers. *Iranian Journal of Pathology*. 2018 Jul 17;13(2):125.
- [14] Park JH, Kwon HJ, Park CS, Hong S. Anaplastic transformation of papillary thyroid carcinoma in a young man: a case study with immunohistochemical and BRAF analysis. *Korean journal of pathology*. 2014 Jun 26;48(3):234.
- [15] Song S, Lee DH, Kim H, Jeong WJ. Coexistent papillary thyroid carcinoma and its anaplastic transformation in cervical lymph node metastasis. *International Journal of Thyroidology*. 2020 May 30;13(1):55-9.
- [16] Zhang Y, Liu Q, Ma D, Maimaiti Y, Ma Z. The coexistence of papillary thyroid carcinoma, anaplastic thyroid carcinoma (squamous cell carcinoma subtype) and poorly differentiated thyroid carcinoma: a case report. *AME Case Reports*. 2024 Apr 7;8:47.

- [17] Shi X, Liu R, Qu S, Zhu G, Bishop J, Liu X, Sun H, Shan Z, Wang E, Luo Y, Yang X. Association of TERT promoter mutation 1,295,228 C> T with BRAF V600E mutation, older patient age, and distant metastasis in anaplastic thyroid cancer. *The Journal of Clinical Endocrinology & Metabolism*. 2015 Apr 1;100(4):E632-7.
- [18] Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JH, Soria JC, Wen PY, Zielinski C, Cabanillas ME, Urbanowitz G, Mookerjee B. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. *Journal of Clinical Oncology*. 2018 Jan 1;36(1):7-13.