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CASE REPORT

WILEY

Post-radiotherapy cribriform-morular thyroid carcinoma

Arzu Or Koca[1] | Gülçin Güler Şimşek[2]

[1]Department of Endocrinology and Metabolism, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Education and Research Hospital, University of Health Sciences, Ankara, Turkey

[2]Department of Medical Pathology, University of Health Sciences, Gülhane Education and Research Hospital, Ankara, Turkey

Correspondence
Arzu Or Koca, Department of Endocrinology and Metabolism, Ankara Dr. Abdurrahman Yurtaslan Onkoloji Training and Research Hospital, University of Health Sciences, Mehmet Akif Ersoy District 13. Street No:56 Postal code: 06200, Yenimahalle, Ankara, Turkey.
Email: drarzuor@hotmail.com

Abstract

Background: According to the new 2022 World Health Organization classification of endocrine tumors, thyroid malignancy, formerly known as the cribriform-morular variant of papillary thyroid carcinoma, is now categorized as differentiated thyroid malignancy; it is, at present, called cribriform-morular thyroid carcinoma and classified as a tumor of unknown histogenesis.

Case Report: In this case report, we report on a 15-year-old patient who underwent external radiotherapy to the neck for Hodgkin's disease and developed cribriform-morular thyroid carcinoma 5 years after radiotherapy.

Conclusions: We believe that cribriform-morular thyroid carcinoma with diffuse nuclear beta-catenin expression has exciting and unresolved uncertainties that may affect disease prognosis and follow-up for cytopathologists and endocrinologists.

KEYWORDS
cribriform-morular thyroid carcinoma, post-radiotherapy thyroid carcinoma, thyroid carcinoma

1 | INTRODUCTION

Cribriform morular thyroid carcinoma is a rare thyroid malignancy with unidentified etiopathogenesis. It has been observed that studies in the literature about this type of thyroid carcinoma with related case series are limited. In this case report, a case of cribriform morular thyroid carcinoma that developed after external radiotherapy to the neck is presented.

2 | CASE PRESENTATION

A 15-year-old female patient was admitted to our clinic in November of 2021 with a thyroid nodule detected on neck ultrasonography (USG). Previously, she received systemic chemotherapy and neck-abdominal radiotherapy for Hodgkin's disease in 2016. The patient, who was cured with lymphoma treatment, was taking 200 mcg of levothyroxine sodium daily due to hypothyroidism developed after radiotherapy treatment. She was not taking any other medication, smoking, or drinking alcohol. She was also undergoing neck USG scanning four times a year due to radiotherapy applied to the neck. A USG scan performed in October 2021 revealed a 3.5×3.5×4.5 mm nodule with indistinct borders, hypoechoic, lobule contour, and

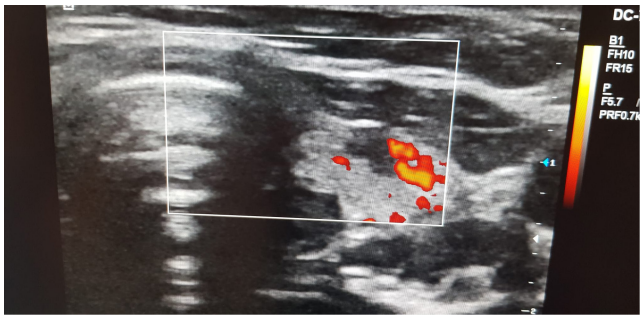

FIGURE 1 Ultrasonographic and color doppler image of a hypoechoic nodule in the left lobe of the thyroid gland.

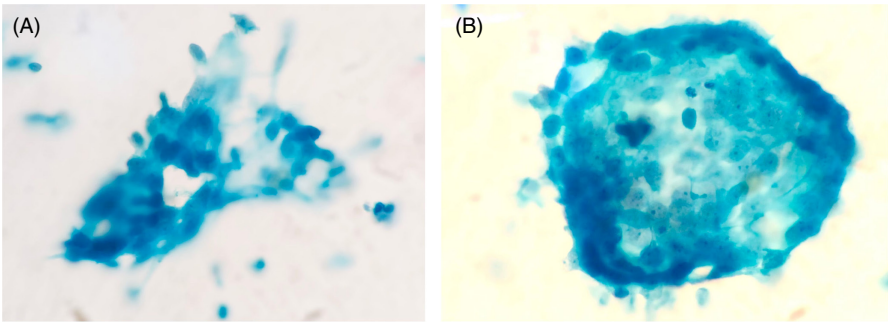

FIGURE 2 (A) Thyroid fine-needle aspiration cytology; cribriform fields (PAP ×1000). (B) Thyroid fine-needle aspiration cytology; squamous morular formation (PAP ×1000).

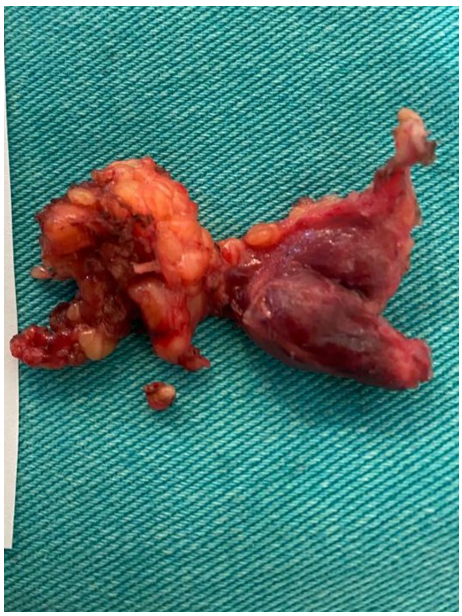

FIGURE 3 Macroscopic image of thyroid left lobe; isthmus.

dense central and peripheral blood supply in the anterior left lobe of the thyroid gland. (Figure 1). In the remaining thyroid gland, the parenchyma was normal, there was no other nodular formation, the right thyroid lobe was 8×8.5×32 mm, the left lobe was 8×7×22 mm, the isthmus was 1 mm, and the thyroid gland volume was decreased. Fine-needle aspiration biopsy of the nodule in the left lobe of the thyroid was reported as "Malignant cytology, compatible with papillary carcinoma." (Figure 2) Left lobectomy, isthmectomy, pyramidal lobectomy, and central lymph node dissection were performed due to the following: the patient had no pathologic lymph nodes detected in the neck USG scan; no family history; was not a smoker; and possibly had a parathyroid gland whose volume may have decreased due to radiotherapy (Figure 3). Postoperative pathology was reported as thyroid papillary microcarcinoma exhibiting the following characteristics: 0.7 cm in diameter; cribriform-morular variant; no tumor on stained surgical margin; lymphatic and vascular invasion; tumor encapsulated and showing invasion to its capsule; no evidence of extra-thyroid spread; one parathyroid gland observed; and nine tumor-free lymph nodes. The patient was genetically examined to screen for possible familial adenomatous polyposis (FAP). Genes associated with non-medullary thyroid cancer (DICER1, FOXE1, MSH2, PRKAR1A, PTENSEC23B, SLC5A5, and WRN), especially APC, were analyzed by next-generation sequencing analysis, and no mutation was found.

The patient's pathology preparations were re-examined after the World Health Organization (WHO) published a new classification set for endocrine tumors in 2022. Histopathologic examination revealed a tumoral lesion (Figure 4) with a cribriform architecture that showed morule formations, prismatic cytoplasm, rare nuclear clefts, and inclusions in the subcapsular area, which were relatively well-demarcated from normal thyroid tissue (Figure 5). Immunohistochemical examination showed focal HBME1 (Figure 6), patchy CDX2 (Figure 7), and diffuse strong beta-catenin expression (Figure 8) in the tumor cells. Cribriformity became prominent with Cytokeratin 19 (Figure 9). No lymphatic, vascular, and/or perineural invasion was detected in the lesion. No metastasis was observed in the nine dissected lymph nodes. The diagnosis was subsequently updated as cribriform-morular thyroid carcinoma.

3 | DISCUSSION AND CONCLUSIONS

Thyroid pathology, formerly known as the cribriform-morular variant of papillary thyroid carcinoma, is now called thyroid carcinoma of unknown histogenesis, according to the new WHO classification of endocrine tumors.[1] Contrary to normal thyroid and other thyroid tumors that show diffuse membranous beta-catenin expression, cribriform-morular thyroid carcinoma appears to have diffuse cytoplasmic and nuclear beta-catenin expression.[2] It is known that these tumors can be observed in cribriform, solid, papillary, long columnar (prismatic), and morular (squamoid) patterns on histopathologic examination and that they are usually well-circumscribed or encapsulated. The cells have eosinophilic cytoplasm and hyperchromatic nuclei with groove and pseudoinclusion. Cribriform-morular thyroid carcinoma can be FAP-associated or sporadic and can exhibit genetic alterations in the Wnt/beta-catenin pathway. APC mutations are the most common genetic alteration and can be found in both familial and sporadic forms.[1]

Cribriform-morular thyroid carcinoma can be described as a very uncommon or partially rare thyroid carcinoma. According to data from the largest case series of these patients (33 tumors), it is mostly seen in the female population and considered to be a disease predominantly affecting young adults (the mean age of occurrence is 33 years).[2] Our patient was diagnosed in a single focus at the age of 15 years. Tumor development after radiotherapy was

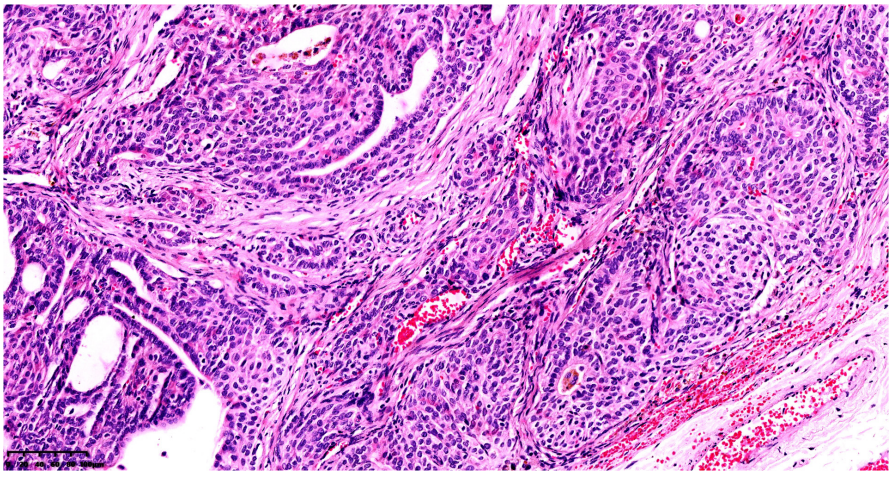

FIGURE 4 Tumoral lesion with rare nuclear clefts and inclusions with prismatic cytoplasm forming follicles, showing morule formations in cribriform architectures (H&E ×400).

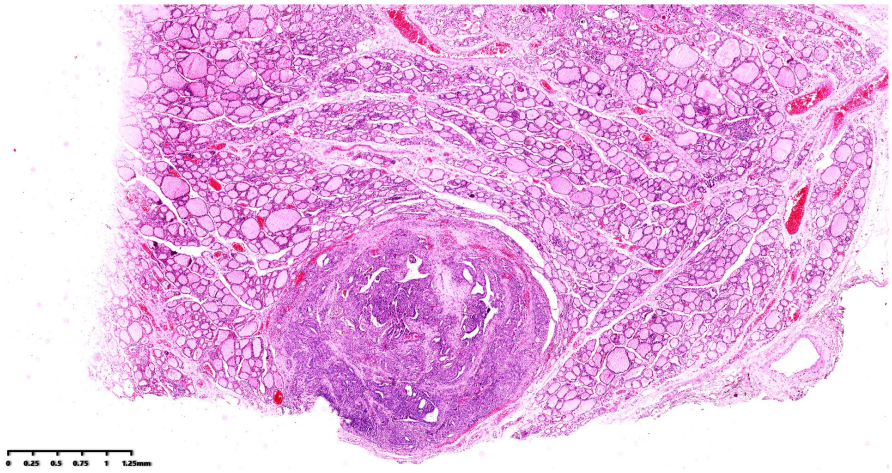

FIGURE 5 Focus of microcarcinoma relatively well-demarcated from normal thyroid tissue (H&E ×40).

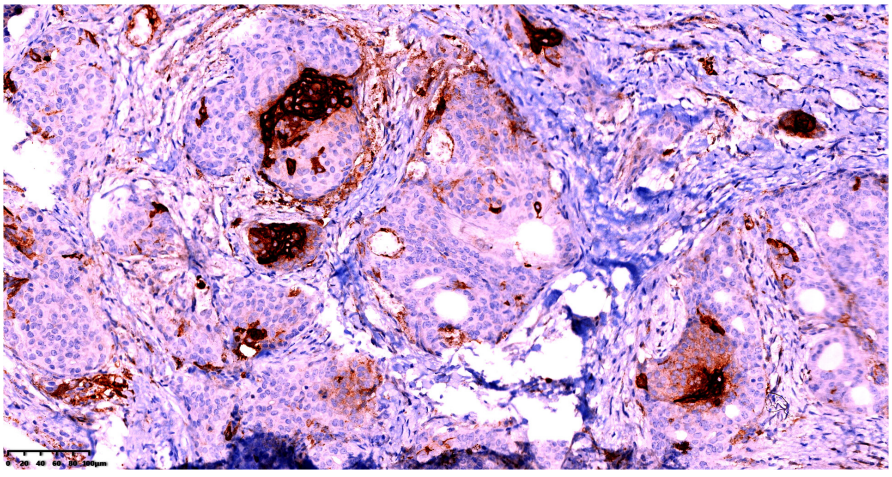

FIGURE 6 Focal patchy membranous HBME1 expression in tumor cells on immunohistochemical examination.

observed in our patient, and this contributes to the literature. The relative risk of thyroid cancer after radiotherapy for Hodgkin's disease is known to be around 14%, and, therefore, long-term screening is performed in cured patients due to the risk of thyroid malignancy.[3] It is known that two-thirds of thyroid malignancies that develop after external radiotherapy are benign and that one-third are malignant and mostly well-differentiated cancers.[4] In a study conducted by Razack et al., the pathologies of patients who received radiotherapy during childhood and developed malignancy were reported as papillary, mixed papillary, and follicular and follicular carcinoma.[5] Hypothyroidism after head and neck radiotherapy, as it developed in our patient, is a well-known and common side effect.[6] However, despite the accumulation of data on the development of thyroid malignancy after head and neck radiotherapy since the 1960s, cribriform-morular cancer (formerly known as cribriform variant papillary cancer) after head

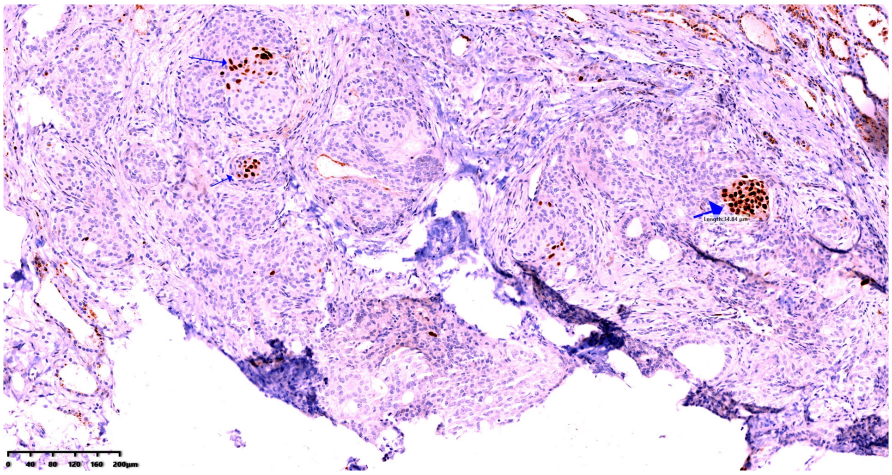

FIGURE 7 Patchy strong nuclear staining in squamoid morule areas with CDX 2.

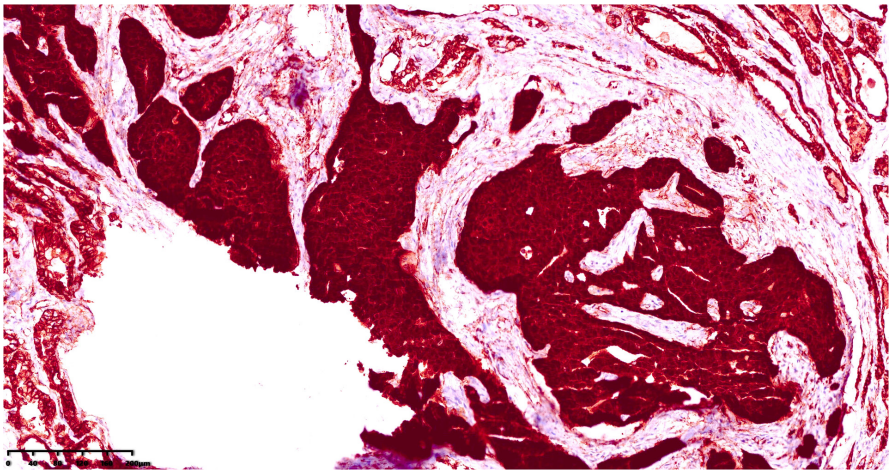

FIGURE 8 Strong cytoplasmic and nuclear staining with beta-catenin in cribriform and morular areas.

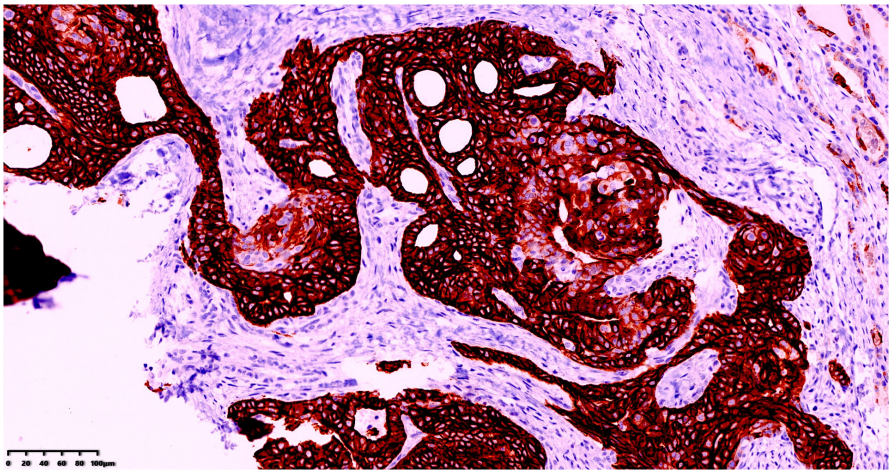

FIGURE 9 Cytoplasmic-membranous staining with CK19 (Cytokeratin 19), revealing cribriformity and morule formations.

and neck radiotherapy has not been reported in the literature. In this respect, our case is a first. In addition, the increased risk of malignancy between 10 and 20 years after radiotherapy manifested earlier (after 5 years).[3] Our patient had no known major risk factors and/or genetic mutations for the development of thyroid malignancy. Literature data show that histopathologic examination findings are nonspecific for radiotherapy-associated thyroid malignancies.[3,5] Thus, the development of cribriform-morular thyroid carcinoma in our patient may be sporadic or due to radiotherapy.

From an endocrinologist's point of view, it can be said that our treatment strategies and the paths needing to be followed in differentiated thyroid cancers have become relatively easier with the increase in knowledge, experience, and guidelines developed day

by day.[7,8] With the disappearance of the cribriform-morular variant papillary cancer designation and the introduction of cribriform-morular thyroid carcinoma of uncertain histogenesis as a new term in the classification of thyroid cancer, the exit from the differentiated cancer classification seems to complicate our work. The lack of conclusive evidence of follicular cell differentiation in cribriform-morular variant papillary cancer raises the possibility that these tumors may not benefit from radioactive iodine-associated adjuvant therapies and eliminates the importance of TSH suppression used in differentiated cancer surveillance.[2]

Cribriform-morular thyroid carcinoma is a relatively rare thyroid malignancy with an uncertain histogenesis, uncertain cell size, and indeterminate risk factors. Radiotherapy-associated cribriform-morular thyroid carcinoma may have developed in our patient, although an exact correlation is not possible under current conditions. We hope that, with an increase in similar case reports and studies in the literature, we will have more information about cribriform-morular thyroid carcinoma.

AUTHOR CONTRIBUTIONS

AOK conceptualized and designed the study, and prepared and edited the article. AOK and GGŞ collected and analyzed the data and finally approved the article.

CONFLICT OF INTEREST

The authors declare no competing interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Arzu Or Koca https://orcid.org/0000-0001-8433-4769

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