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CASE REPORT

# Malignant carcinoma and skin melanoma neoplasms concomitantly in the thyroid

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**Abstract**

Malignant melanomas metastatic to the thyroid gland are uncommon. Based on microscopy and DNA methylation profile, we report a rare coexistence of neoplasms in the thyroid, presumably in our case, with relapse-free condition on adjuvant therapy.

**KEYWORDS**

DNA methylation, malignant melanoma, medullary thyroid carcinoma, prognosis, thyroid

## 1 | INTRODUCTION

The study investigates the case of a total thyroidectomy, where after dissection two nodules showed two distinct immunophenotypes by immunohistochemistry. DNA methylation profile was used to further inspect the origin of the coexisting neoplasms. We confirmed the presence of malignant skin melanoma coexisting with medullary thyroid cancer.

Medullary thyroid cancer (MTC), a neuroendocrine tumor, is the least common histological type of thyroid cancer (about 2%).[1] Contrary to papillary, follicular and anaplastic thyroid cancers, MTC does not emanate from follicular cells but from parafollicular C cells of the thyroid gland, the latter being the major source of calcitonin hormone.[1,2] The latest investigations about the underlying molecular mechanisms of MTC indicate that the presence of RET proto-oncogene mutation is a major significant factor, and that an early detection of this marker will lead to an early diagnosis and treatment, thus favorable prognosis.[2] Nevertheless, not all thyroid tumors harbor RET mutation, it accounts most of the hereditary cases and only some of the sporadic ones.[2] In both cases, the accepted treatment is total thyroidectomy.[1] After surgery, follow-up care for patients implicates monitoring the blood levels of calcitonin or carcinoembryonic antigen (CEA).[1] Today, despite advances in treatment, some cancer patients still develop aggressive relapse and serious tumor behavior such as concurrent onset of melanoma leading to death.[1,3–5] Usually, metastatic melanomas are reported with a primary site such as cutaneous, ocular, or visceral.[5,6] Except in some cases of cancer

of unknown primary site, the melanoma might possibly arise as a second primary in association with the first tumor.[5,7–10] From a biological point of view, besides the hypothesis of de novo onset within different sites, some studies explain melanomas of unknown primary as being the result of a regression of the primary tumor after the occurrence of the metastasis, mediated by the immune system.[11] Nevertheless, during carcinogenesis, cell dysregulation could cause malignant cells to express other tissue-specific markers or metabolites which would make distinguishing its tumor of origin more difficult.[12] In the present study, we investigate further the occurrence of malignant melanoma concomitant with MTC in the thyroid, which constitutes a rare new association of neoplasms. The development of novel molecular techniques such as mass spectrometry imaging, next-generation sequencing (NSG), and epigenetic profiling for the classification of cancer of unknown primary has contributed to the interest in elucidating the origin of the two coexisting neoplasms.[13–15] This might help in predicting survival outcome that is associated with primary tumor origin.[16] In addition, such elucidation will guide for the best therapeutic choice.[13] Hence, a tumor-specific therapeutic agent will result with better prognostic outcomes.[13] To our knowledge, no study has deepened the diagnosis of such rare association of neoplasms, most likely in our case, characterized by a more stable condition compared to melanomas.

## 2 | CASE REPORT

A 68-year-old Lebanese lady, with no past medical history, was admitted to the department of surgery at Al Rassoul Al Aazam Hospital (RAH). The patient had a chief complaint of neck mass in the posterior triangle. She presented to our hospital with a painless neck swelling. Submandibular lymph nodes were not enlarged, and the rest of the examination was unremarkable. Upon presentation, she was on no medications. After normal chest X-ray, abdominal computed tomography (CT) scan, and laboratory studies, an endoscopic exploration showed severe thyroid mass with a tracheal deviation to the left side. A total thyroidectomy was performed. Grossly, the resected thyroid mass, weighting 280 g, revealed upon sectioning multinodular goiter and one black nodule measuring 12 × 11 × 10 cm (Figure 1). The two nodules were completely separated with no common anatomy. Fibroadipose tissue and all paratracheal and lateral lymph nodes were removed. Microscopy showed two different malignant neoplasms in the resected thyroid, with hyperplasia as a background disease. The first tumor was identified as medullary carcinoma of the thyroid and the second one as highly suspicious to be a malignant melanoma. This latter consisted of anaplastic epithelioid cells with prominent melanin pigments. Both tumors were within thyroid parenchymal tissue (Figure 2). Lymph nodes appeared to be reactive and/or metastatic (Figure 3). A chest wall lesion measuring 1 × 0.5 × 0.4 cm was investigated and was shown to be benign aggregates of blood vessels consistent with hemangioma. Clinical status and imaging confirmed the absence of any possible primary site or metastasis of the melanoma neoplasm. Tumor medullary carcinoma cells showed positivity for synaptophysin, TTF-1, and calcitonin with a low signal (5%) for Ki-67 proliferation marker; whereas tumor melanoma cells stained focally up to 15% for Ki-67 and expressed S100, Melan A, and HMB-45. Molecular analysis indicated that the patient was negative for BRAF oncogene mutation. Epigenetic findings, based on microarray DNA methylation signature, classified a first neoplasm as skin cutaneous melanoma discarding the other 37 tumors of EPICUP database. The test was repeated on DNA extracted from sections partially coincident with the first processing; the prediction was skin cutaneous melanoma as well. A third assay was performed on areas other than those included in the two preceding processings that corresponds to the second neoplasm specifically. In this analysis, it was not possible to get a specific prediction because no statistically significant similarities were found within the 38 tumor types included in EPICUP

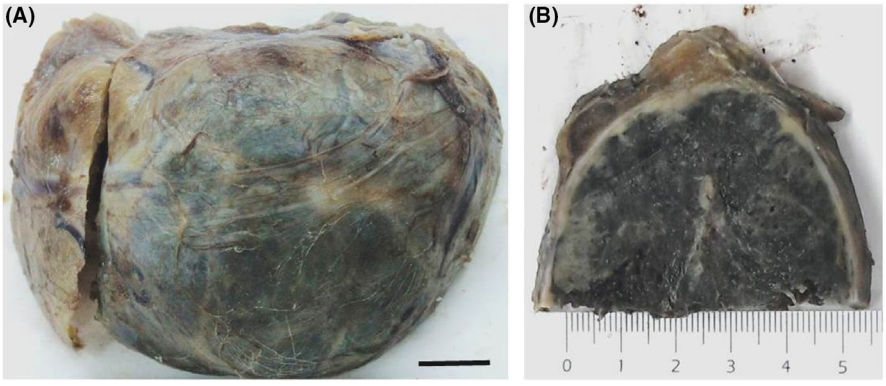


**FIGURE 1** Gross image of the thyroid nodule. (A) Shows a macroscopic outer surface (bar = 1 cm). (B) Shows a macroscopic cut surface demonstrating the deposition of a diffuse black discoloration

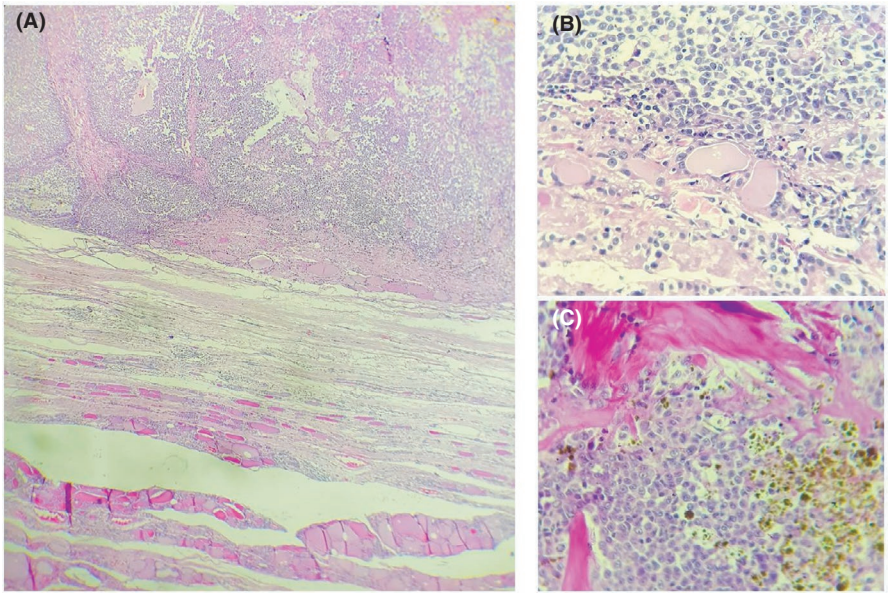


**FIGURE 2** Histologically, hematoxylin and eosin staining revealed a (A) neoplasm capsule and adjacent thyroid tissue (magnification, ×40), a (B) malignant melanoma infiltrating thyroid follicle (magnification, ×400), and (C) malignant melanoma cells with clear brownish deposition (magnification, ×400)

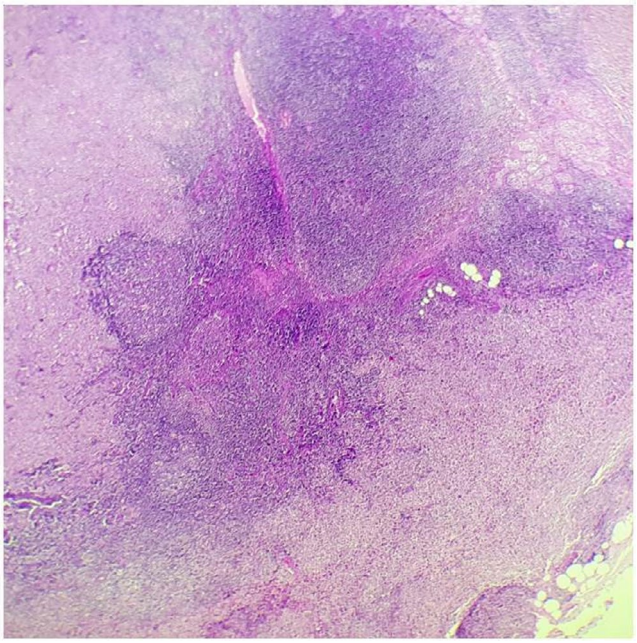

**FIGURE 3** Histologically, hematoxylin and eosin staining of metastatic malignant melanoma lymph node (magnification, ×40)

database, discarding all these tumor types (comprising papillary and follicular thyroid carcinoma) with specificity above 99.9%; but not eliminating medullary thyroid carcinoma. The case was thus confirmed to be a malignant skin melanoma concurrent with a medullary thyroid carcinoma. Postoperatively, the patient was put on immunotherapy, namely Nivolumab, following clinical practice guidelines. Eighteen months later after continuous follow-up, the patient maintained a relapse-free status coupled with negative findings on PET (positron emission tomography), CT, and ECHO.

## 2.1 | Tissue preservation

The resected thyroid organ was formalin-fixed, and paraffin-embedded blocks were stored at the Department of Pathology at Al Rassoul Al Aazam Hospital. A clinical photograph was obtained with written permission kept in the patient's medical chart.

## 2.2 | Histophathological evaluation

Different tissue sections from the nodules were cut, stained, and examined by light microscopy to determine the presence of tumor cells and their morphological appearance. Hematoxylin and eosin-stained slides (H&E) were performed according to a standard protocol.

## 2.3 | Mutational analysis for BRAF

Tumor sample was analyzed for the presence of BRAF mutation by reverse transcription-polymerase chain reaction (RT-PCR). BRAF mutation testing was performed at Institut National de Pathologie, Baabda, Lebanon (INP).

## 2.4 | Immunohistochemistry

Immunostaining was performed according to a standard protocol with commercially available antibodies at the American University of Beirut Medical Center, Beirut, Lebanon (AUBMC), a CAP-accredited laboratory service.

### 2.5 | Microarray DNA methylation

EPICUP (Ferrer) testing was performed to help identify the primary tumor in sample with cancer of unknown primary. This epigenetic technique has been developed and clinically validated using over 10,000 oncology patient samples, achieving overall sensitivity and specificity results of 96.7% and 99.9%, respectively.[13] DNA from paraffin-embedded blocks was processed using the EZNA FFPE DNA kit (Omega Bio-tek). The DNA was then distributed in a 96-well plate and processed with the EZ-96 DNA Methylation Kit (Zymo Research Corp). Bisulfite-converted DNA (bs-DNA) was performed following the Infinium FFPE restoration guide (Illumina). Microarray hybridization and scanning were done as previously described.[13] Raw data were normalized using the lumipackage available for bioconductor, within the R statistical environment. Methylation levels of 485,577 CpG sites were determined. Variance analysis was done after categorization of the sample into one of the 38 tumor types of EPICUP. $p$ value was adjusted with the Bonferroni method and Tukey's honest significant difference post hoc test. CpG that was specific for at least one tumor type was selected ($p < 0.01$). The test and analysis were repeated three independent times and carried out by the Cancer Epigenetics and Biology Program (PEBC) of the Bellvitge Biomedical Research Institute (ISO13485-accredited), Catalonia, Spain.

## 3 | DISCUSSION

The thyroid gland is one of the classic neuroendocrine organs.[1,17] Its carcinoma is classified into medullary, papillary and follicular, and represents the most common type of endocrine-related cancer with an estimated prevalence of 3.1% among all new cancer cases.[2,15,17] Metastatic melanomas can occur in any region of the body and pose variable prognosis based on the mutation profile.[5,6,8–10,18] Knowledge about the histopathology, immunohistochemical as well as ultrastructural features can provide important clues.[12,18] For the present study, our comprehensive immunohistochemistry profiling revealed the presence of two tumor types in the thyroid, a malignant melanoma, and a medullary carcinoma. The molecular investigation for mutation analysis was essential for the diagnosis. BRAF gene, encoding a protein that belongs to the RAF family of serine/threonine protein kinases, is often mutated in a number of cancers including thyroid carcinomas and mainly melanomas.[18] This protein is responsible for regulating the MAP kinase/ERK signaling pathway, hence affecting cell division, differentiation, and secretion.[18] The occurrence of mutation in this gene has been correlated with aggressive melanoma cases.[18] Targeted therapies designed to treat cancers with such mutation are found to be well effective.[18] In our case, the patient was negative for BRAF, which presented a diagnostic dilemma. The melanoma was hard to be distinguished between being a new primary or a distant metastasis; mainly that a tumor type-specific therapy would definitely increase the patient survival compared to an empiric therapy.[13,19] Kung et al. reporting a case of melanoma to the thyroid, without a secondary neoplasm, suggested that patients with such profile are to be considered as having metastasis until proven otherwise.[19] Actually, in the literature, supportive evidenced recent cases of melanoma metastatic to the thyroid are found.[10] Fibbi et al. described a synchronous presence of medullary and papillary carcinoma with a non-metastatic cutaneous melanoma that latter being easily detected as suspicious nevus 7 months post-therapeutic surgery.[2] Interestingly, the papillary carcinoma and the melanoma were positive for BRAF mutation.[2] To the best of our knowledge, similar to our work only two prior studies have reported the coexistence of melanoma with MTC with no other primary.[20,21] A third study with comparable histophathological evaluation to our work, reported undoubtful conclusion on the occurrence of a melanin-producing MTC after genetic testing using standard PCR.[22] Yet, none of these mentioned studies did further molecular investigation about the origin of neoplasms. Currently, it is proposed that this occurrence is presumably due to an immune-mediated regression of the primary origin after metastasis has occurred.[3,11] Studies reported the presence of atypical skin discoloration as evidence.[11] This suggestion is an interesting most likely explanation, albeit no pigmented clinical lesion was observed in our investigation demonstrating a regressive pattern of a primary origin. Singh et al. assembled and reviewed many old reported cases of MTC with black deposits proposing it to be melanin-producing MTC and emphasizing on the fact that it could be differentiated from metastatic or de novo melanoma based on the morphological features and biomarkers.[12] However, detailed investigations were lacking. These cases were quite different from that of our patient because the black nodule found in the thyroid was distant from the nodules having the thyroid carcinoma cells, besides that morphologically the melanin-containing neoplasm was consistent with malignant melanoma. With the evolution of molecular techniques, DNA methylation profile is reported to be specific for each type of cancer.[13] Here, we present our investigation for the DNA methylation pattern of both neoplasms and conclude about their origin. The first correlated best with an MTC and the second with a skin cutaneous melanoma. The findings

of this investigation showed that epigenetic analysis is crucial for cases with coexistence of tumors mainly those with unknown primary. This is the first study reporting a concomitant MTC and skin melanoma that was further diagnosed with epigenetic analysis. The patient was successfully treated with nivolumab, a human IgG4 antibody inhibiting the interaction of PD-1 (programmed death 1) receptor with its ligands.[23,24]

In conclusion, we report an epigenetic evidence of a concomitant malignant carcinoma and skin cutaneous melanoma, with no other primary, in the thyroid of a patient who was treated with nivolumab and maintained a relapse-free clinical status for more than 18 months after surgery.

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## CONFLICTS OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

All the authors have contributed to this manuscript. AA-H and JC have performed the surgery and helped in correcting the manuscript. ID has contributed to the design and writing of the manuscript. HM has managed the clinical status and follow-up of the patient and helped in correcting the manuscript. MS and HY have performed the pathological sections and image analysis. FA, HK, and MY have helped in correcting the manuscript. We confirm that all authors have read and approved the final version of the manuscript.

## ETHICAL APPROVAL

The current case report was approved for publication by the Institutional Review Board of RAH, and the patient data used in this study were anonymized. The patient gave his signed informed consent for this study as well as the analysis reported in this paper. The study was conducted in accordance with the Declaration of Helsinki.

## CONSENT

Published with written consent of the patient.

## DATA AVAILABILITY STATEMENT

Data are available when applicable.

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