Case Report

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Medullary Thyroid Carcinoma Showing Melanocytic Differentiation: A Report of a Rare Case

Melanositik Diferansiasyon Gösteren Tiroid Medüller Karsinomu: Nadir Bir Olgu Sunumu

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Abstract

Medullary thyroid carcinoma (MTC) accounts for 5-10% of all thyroid malignancies. These tumors show variable morphological features, however, to the best of our knowledge, melanocytic differentiation is rare with only 11 reported cases. We report a 44-year-old female who presented to our clinic with neck swelling of a few months. The thyroid fine needle aspiration biopsy results were suspicious, leading to a total thyroidectomy. On microscopic examination, a malignant tumor with melanocytic features was seen. There was no amyloid deposition in the stroma. Immunohistochemical analysis revealed that the tumor cells were positive for calcitonin, melan-A, HMB45, pancytokeratin, chromogranin, carcinoembriyonic antigen; focal positive for S-100; and negative for HBME-1 and thyroglobulin. This tumor was diagnosed as medullary carcinoma with melanocytic differentiation when evaluated with the morphological and immunohistochemical findings. *Turk Jem 2015; 19: 72-75*
Key words: Thyroid, medullary carcinoma, pigment, melan-A

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Özet

Tiroidin medüller karsinomu (TMK) tüm tiroid malignitelerinin %5-10'nunu oluşturmaktadır. Değişik morfolojik özellikler taşıyabilen bu tümörlerde melanositik diferansiyasyonlu varyantlar oldukça nadir olup, bildiğimiz kadarıyla şu ana kadar literatürde sadece on bir olgu yayınlanmıştır. Bu sunumda, son aylarda boynunda şişlik yakınması ile kliniğe başvuran 44 yaşında kadın hasta anlatılmaktadır. Tiroid ince iğne aspirasyon biyopsisinin kuşkulu olarak değerlendirilmesi üzerine, hastamıza total tiroidektomi yapıldı. Mikroskobik olarak melanositik özellikler taşıyan malign tumor dikkati çekti. Stromasında amyloid birikimi saptanmadı. İmmünohistokimyasal incelemede tümör hücrelerinde kalsitonin ,melan-A, HMB45, pansitokeratin, kromogranin, karsinoembriyonik antijen pozitif, S-100 fokal pozitif, HBME-1, tiroglobülin negative saptandı. Morfolojik ve immunhistokimyasal bulgular eşliğinde bu tumor tiroidin melanositik differansiyasyon gösteren medüller karsinomu olarak değerlendirildi. *Turk Jem 2015; 19: 72-75*
Anahtar kelimeler: Tiroid, medüllerkarsinom, pigment, melan-A

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

Introduction

Medullary carcinoma of the thyroid constitutes 5-10% of all thyroid malignancies. The tumor derives from parafollicular C cells of neural crest origin (1,2,3). The tumor presents variable morphological features and follicular and papillary variants in addition to small cell, giant cell, clear cell, oncocytic, squamous and melanocytic variants (4). Medullary carcinoma with melanocytic differentiation has first been reported by Marcus et al. and is a rare variant with only 11 reported cases so far (2,5,6). Medullary thyroid carcinoma (MTC) tumors can release many hormonal and nonhormonal products (gastrin-releasing peptide, somatostatin, ACTH, keratin, beta-endorphin, corticotropin-releasing hormone-like peptide, serotonin, substance P) in addition to melanin pigment (7,8).

Case Report

We report a 44-year-old female who presented with neck swelling of a few months. The thyroid fine needle aspiration biopsy results were suspicious, leading to a total thyroidectomy.

Macroscopic evaluation of the specimen revealed a dark brown solid tumor 3.5 cm in diameter with a thin capsule in the right

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thyroid lobe that was separated from the thyroid tissue with a regular border. Microscopically, the tumor was separated from the surrounding thyroid tissue with a thin fibrous capsule. Thin fibrous bands created a nodular structure and the tumor consisted of cells that were spindle-shaped or pleomorphic in various parts of the tumor with an organoid pattern and contained brown pigment in their cytoplasm and the intercellular distance, which could be seen even on low magnification (Figure 1, 2). No amyloid deposition was seen in the tumor stroma. Tumor invasion was present in a blood vessel within the tumor capsule. Immunohistochemical (IHC) analysis revealed that the tumor cells were positive for calcitonin, melan-A, HMB45, pancytokeratin, chromogranin, carcinoembriyonic antigen; focal positive for S-100; and negative for HBME-1 and thyroglobulin (Figure 3).

Due to intense melanocytic features, probability of BRAF mutations was evaluated. DNA isolation was performed from FFPE tissue sections with QIAamp DNA FFPE Tissue Kit according to the manufacturer's instructions (Qiagen, US). The DNA sample was tested using EntroGen's B-RAF mutation analysis kit (EntroGen, US). This test is a real-time PCR assay that uses allele specific primers that are complementary to mutant variants of the BRAF gene codon 600. No mutation was detected in our sample.

The tumor was diagnosed as medullary carcinoma with melanocytic differentiation when evaluated with the morphological and IHC findings. No C cell hyperplasia was seen in the surrounding thyroid tissue. The serum calcitonin was undetectable before the surgery and was within normal limits (2.2 pg/ml) afterwards. There was nothing of significance in the family history. We did not come across any pigmented skin lesion suspicious for malignant melanoma during the physical examination. Positron emission tomography revealed a lesion extending longitudinally within the anterolateral muscular structures of the right thigh with FDG enhancement (SUV max: 4.21). This lesion had been interpreted as proliferative myositis at another center. Diffuse distant organ metastases (liver, breast, neck region) were found approximately four months after thyroidectomy during follow-up, and the patient died six months after the first surgery.

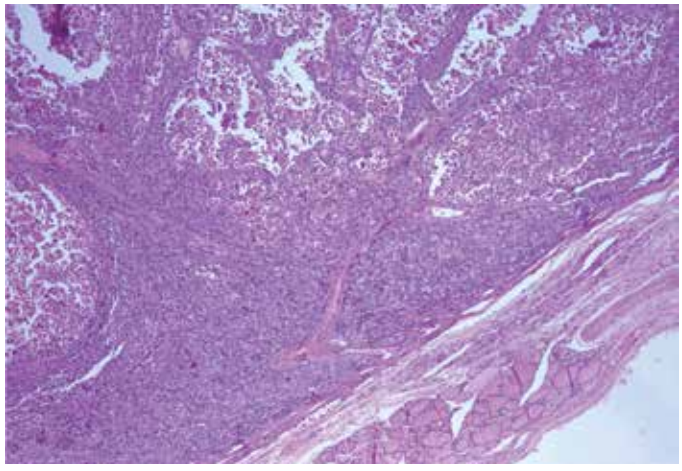

Figure 1. Normal thyroid tissue in the lower right and the tumor that is separated with a thin capsule are seen. The tumor consists of solid areas that are cohesive or spindle-shaped in parts and separated by fibrous bands (HE&4)

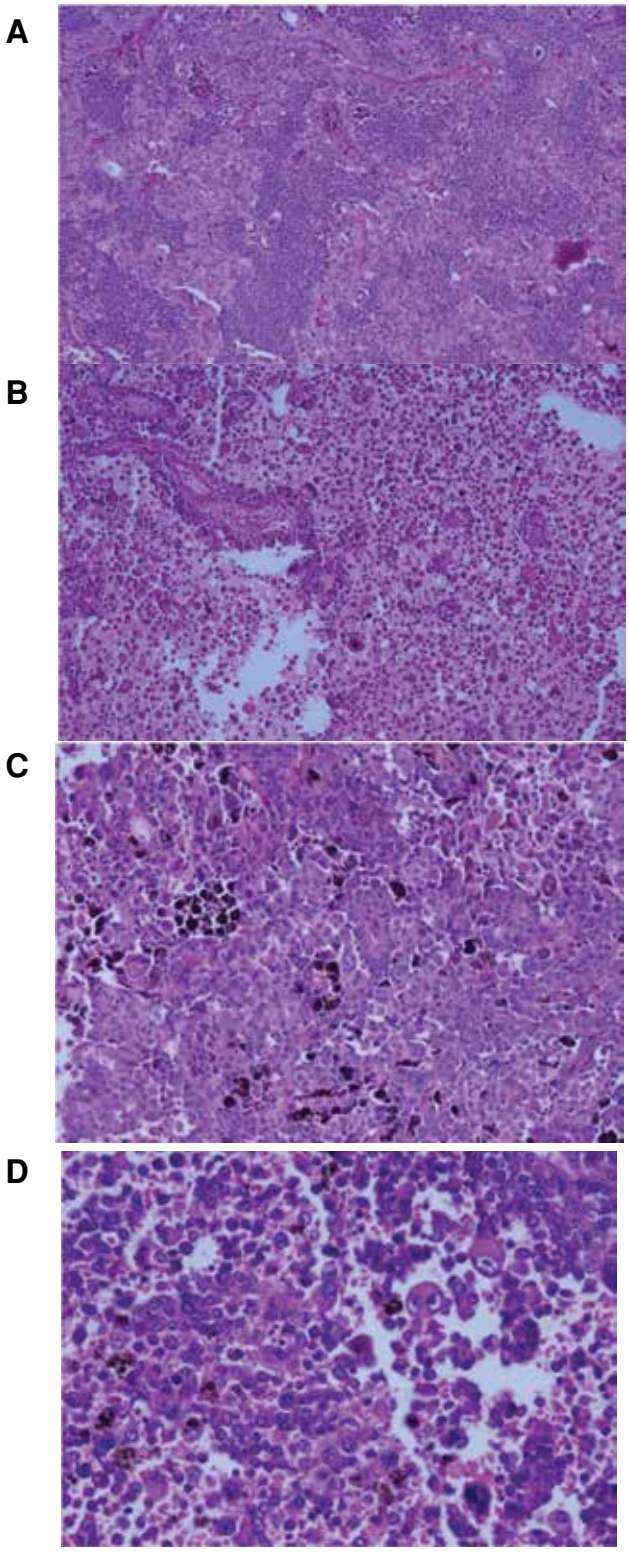

Figure 2. A) Areas with narrow cytoplasm, spindle-shaped tumor cells in the darker violet areas together with pleomorphic tumor cells that have a pink and wide cytoplasm (HE&original magnificationx10). **B)** Dyscohesive pleomorphic tumor cells and cytoplasmic melanin pigment (HE&original magnificationx10). **C)** Tumor cells, some spindle-shaped, with dense melanin pigment (HE&original magnificationx20). **D)** Closer appearance of tumor cells (HE&original magnificationx40)

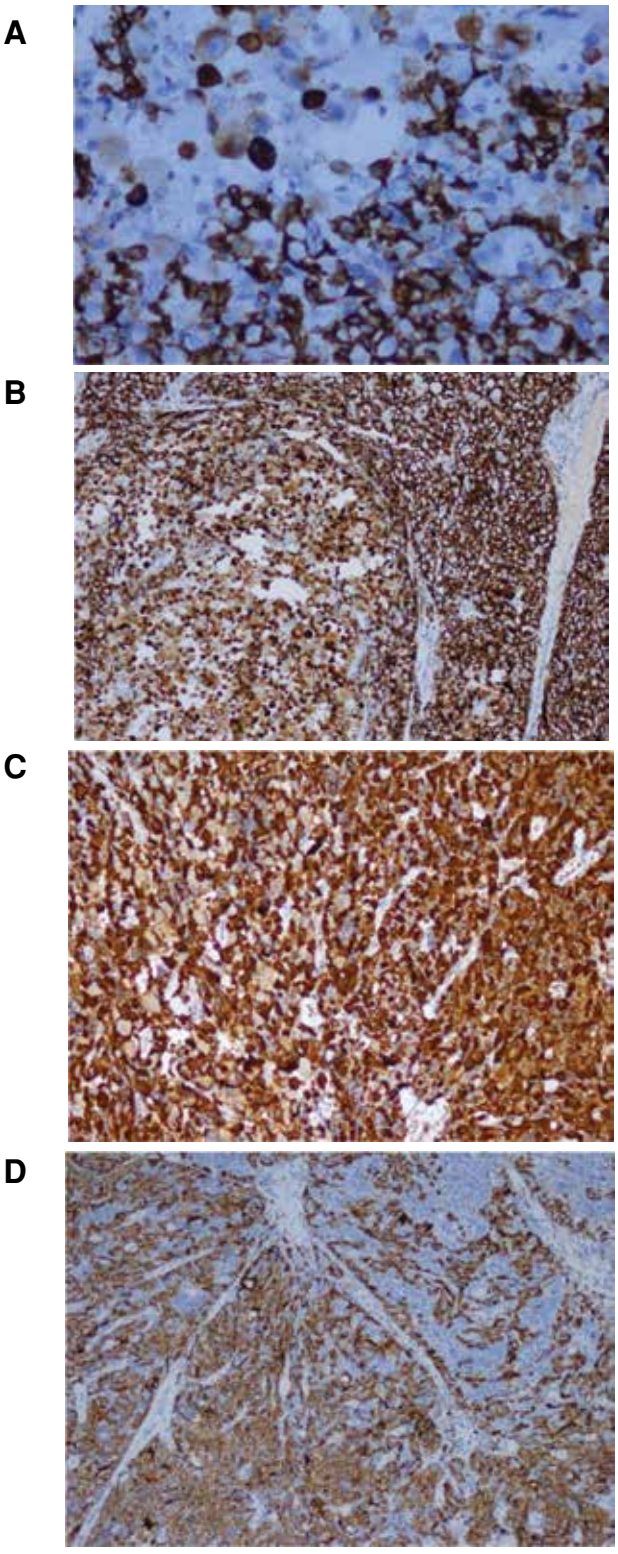

Figure 3. Tumor cells are. **A)** HMB45 positive (original magnificationx40), **B)** Melan-A positive (original magnificationx10), **C)** Calcitonin positive (original magnificationx20) and **D)** pancytokeratin positive (original magnificationx10) on immunohistochemical evaluation

Discussion

Multivariate differentiation of tumor cells in medullary carcinoma is already recognized but melanocytic differentiation is very rare. Melanin deposits in the tumor cell cytoplasm and stroma varies from case to case and from area to area in the same case. In our case, the tumor was separated from the surrounding thyroid tissue with a thin fibrous capsule. A nodular structure had developed with fibrous bands separating from the capsule in some foci. The tumor had pleomorphic features morphologically and also showed variety of features of malignant melanoma. Marked cytoplasmic and intercellular dark brown pigment was observed. The first consideration should be malignant melanoma metastasis in case of a pigmented tumor in the thyroid, as with any organ in general. The possibility of malignant melanoma metastasis should therefore first be fully eliminated. However, this is quite rare (4). Malignant melanomas of the head and neck region make up 20% of all malignant melanoma cases (2). Ectopic melanin pigment production is rare in neuroendocrine tumors other than MTC (3,5,6,8).

The parafollicular C cells of neural crest origin that make up MTC can differentiate in various ways. Calcitonin is a marker specific for parafollicular C cells and calcitonin positivity in these tumors therefore indicates an MTC with melanocytic differentiation (2).

MTC may be one of the first pathologies to consider in the differential diagnosis when calcitonin is measured with a clinical suspicion of MTC. However, the presence of a single nodular lesion with a thin capsule and a surrounding regular border separating the lesion from normal tissue may indicate a primary thyroid malignancy at first when the calcitonin level has not been measured preoperatively. Our case had no family history of thyroid malignancy and there was no C cell hyperplasia within the thyroid parenchyma surrounding the tumor.

Amyloid deposits are seen at rate of 75% in conventional MTC (1). This leads to no difficulty in the differential diagnosis for medullary carcinomas with melanocytic differentiation and amyloid deposits (3). However, other supportive features are needed in cases like ours where there are no amyloid deposits.

IHC analysis in our case revealed that the tumor cells were positive for calcitonin, melan-A, HMB45, pancytokeratin, chromogranin, and carcinoembriyonic antigen, focal positive for S-100, and negative for HBME-1 and thyroglobulin. Calcitonin is one of the best and most specific markers for MTC. Chromogranin also possesses similar features. HMB45 is important for evaluation of melanocytic differentiation (3,4,6,7). HMB45 staining is present in melanomas, tumors with melanocytic differentiation, and junctional and blue nevi while there are no data on cross reaction in MTC cases (4). In conclusion, the staining with these markers has made it easier for us to make the diagnosis.

The prognostic features of this rare variant, which are first defined by Marcus et al., are not known but a possible more aggressive behavior has been emphasized (5,6). Our case similarly showed multiple distant organ metastasis four months after thyroidectomy. This rare variant of medullary carcinoma should be considered

when there is a suspicion of malignant melanoma metastasis to the thyroid with the morphological features.

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