



## Original Article

# The relationship of melanocytic differentiation with prognostic markers in medullary thyroid carcinomas



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## ABSTRACT

**Introduction:** Medullary thyroid carcinoma (MTC) makes up 5–10% of thyroid malignancies. Small cell, squamous, giant cell or melanocytic differentiation can rarely be seen in MTCs. It is important to determine those with the potential to act aggressively such as cases with melanocytic differentiation at the time of diagnosis.

**Materials and method:** A total of 46 MTC cases diagnosed at four different centers between 2002 and 2013 were included in the study. Immunohistochemical (IHC) staining with Melan-A and HMB-45 was performed in all cases.

**Results:** Six of the 46 MTC cases were medullary microcarcinomas and three were multicentric medullary carcinomas. There were 34 females and 12 males with a mean age at onset of 51.4 years and mean tumor diameter of 23.2 mm. Lymph node metastasis (LNM) was found in 13 of the 38 cases that had data regarding the lymph nodes. Immunohistochemically, Melan A staining was seen in four cases. HMB45 staining was seen in four cases. A statistically significant relationship was found between LNM and diameter, Melan A expression ( $p = 0.02$ ,  $p = 0.03$  respectively) but there was no significant relationship with HMB45 expression ( $p = 0.07$ ). General survival data were present for 35 of the 46 cases. All cases without lymph node metastasis survived (21/21) while 8 of 11 cases with lymph node metastasis survived among cases with survival data; one case that was diffuse-strong positive for both HMB45 and Melan A was lost due to distant organ metastasis six months after the diagnosis.

**Discussion:** Should the possibility of melanocytic differentiation be evaluated in cases where melanocytic differentiation is not reflected in the morphology (lack of pigment) in MTCs? We did not come across a study on the subject in the English literature. The effect of melanocytic differentiation on the prognosis in MTCs should be investigated in larger series.

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## Introduction

Medullary thyroid carcinoma (MTC) makes up 5–10% of thyroid malignancies and 80% are sporadic. It develops from parafollicular C cells and is usually located in the upper and middle regions of the thyroid lobes [1–3]. Although the macroscopic features are

not typical, it has microscopical identifying morphological features. Cords formed of spindle-shaped, round or polygonal cells are noted in a fibrous-hyaline, amyloid-containing (70%) stroma in most cases [1]. Tumor cell cytoplasm is large with an eosinophilic and fine granular structure. Although different morphological variants (small cell, giant cell, squamous, melanocytic differentiation) are defined [4], immunohistochemical (IHC) and molecular features not reflected in the morphology may be present. MTCs show an immunohistochemical positive reaction with calcitonin, chromogranin, CEA and TTF1.

The most important factor for defining MTC prognosis is the clinical stage at the time of diagnosis [5]. Prognosis is excellent in cases without metastasis. The possibility of central and cervical lymph node metastasis increases with increased tumor diameter

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[6]. Distant metastases are primarily observed in the liver, lung and bone [7].

The familial non-MEN associated group has the best prognosis and cases with MEN 2B the worst. Female sex, age under 40 years, a tumor stroma containing intensive amyloid and calcitonin positivity in more than 75% of the cells are good prognostic signs [5,7]. We investigated the expression of melanocytic markers with the immunohistochemical method in MTCs and determined whether there was a relationship between melanocytic differentiation and prognostic markers, a subject that has not previously been clearly evaluated in the literature.

## Materials and method

### Patient and tissue selection

A total of 46 MTC cases diagnosed at Şifa University's Pathology Department, the Private Ege Pathology Laboratory, Izmir Tepecik Training and Research Hospital Pathology Department and the Micro Private Pathology Laboratory between 2002 and 2013 and whose paraffin blocks with tumor were available were included in the study.

### The evaluation parameters used for immunohistochemical staining

Immunohistochemical Melan-A and HMB45 expression was investigated in all cases. Morphological and immunohistochemical features were evaluated by two pathologists (SK, FNI) at different times. Cytoplasmic staining was considered positive for both antibodies. Staining prevalence was evaluated as focal or diffuse, and the severity as weak or strong.

### The analysis of statistical data

Statistical analyses were performed with the SPSS (Statistical Package for Social Sciences) Windows 18.0 program. In addition to descriptive statistical methods, the Chi Square Test and Fisher's Exact Test were used in the comparison of categorical variables. Binary numerical data were compared with the Mann-Whitney *U* Test. Survival data were obtained with the Kaplan Meier, Log Rank and Cox Regression analyses. A *p* value <0.05 was accepted as statistically significant.

## Results

### Clinical and pathological parameters

There were 34 females and 12 males with a mean age of 51 (28–79) years. The mean tumor diameter was 2.3 (0.2–7) cm. Six cases were microcarcinomas. We noted C cell hyperplasia in 9 cases of which 2 were multicentric, 4 were microcarcinoma and 2 had additional parathyroid adenoma. Lymph node data were present for 38 cases; lymph node metastasis was present in 13 and absent in 25 cases. There was no statistically significant relationship between lymph node metastasis (LNM) and age or multicentricity (*p* = 0.95, *p* = 0.97 respectively) but a significant relationship was present between LNM and increasing diameter (*p* = 0.02, Table 1). A statistically significant relationship was found between LNM and Melan A expression (*p* = 0.03, Table 2) but none between LNM and HMB45 expression (*p* = 0.07). We did not observe Melan-A and HMB45 positivity in multisentric cases and cases with C cell hyperplasia.

General survival data were present for 35 cases. The mean follow-up duration was calculated as 41.4 (6–132) months. Thirty of the cases survived. All patients with medullary microcarcinoma

**Table 1**

The relation between diameter and lymph node metastasis (*p* = 0.023).

	Lymph node metastasis	N	Mean rank
Diameter	–	25	15.18
	+	9	23.94
Total		34	
Diameter			
Mann-Whitney <i>U</i>		54,500	
Wilcoxon <i>W</i>		379,500	
Z		–2268	
Asymp. Sig. (2-tailed)		.023	
Exact Sig. [2*(1 – tailed Sig.)]		.022 (a)	

were alive. All 21 cases without lymph node metastasis and 8 of the 11 cases with lymph node metastasis, among patients with lymph node data survived. No statistically significant relationship was found between lymph node metastasis (*p* = 0.11), age (*p* = 0.63), tumor size, (*p* = 0.08), gender (*p* = 0.74) and general survival. Among cases with survival data, 2 HMB45 weak positive cases and 1 Melan-A weak positive case survived while 1 HMB45 and Melan A diffuse-strong positive case was lost due to distant organ metastasis six months after the diagnosis.

### Immunohistochemical staining results

Melan A staining was diffuse-strong in one case, diffuse-weak in one case and focal-weak in two cases on immunohistochemical investigations with no staining being found in the remaining 42 cases (Figs. 1 and 2). HMB45 staining was diffuse-strong in one case and focal-weak in three cases (Fig. 3). All remaining cases were HMB45 negative. HMB45, Melan-A positivity was not observed in cases showing C cell hyperplasia. There was no sign suggesting melanocytic differentiation in H&E-stained preparations except for one case with intense dark brown pigment (Fig. 4).

Lymph node metastasis was observed in three of four cases with diffuse or focal Melan A staining. The detailed pathology data of the remaining case could not be accessed. Lymph node metastasis was found in three of the four HMB45 positive cases. The relationship between LNM and Melan-A expression was statistically significant (*p* = 0.03) but a similarly significant relationship was not present between LNM and HMB-45 (*p* = 0.07). Although the number of cases is low, no statistically significant relationship was found between HMB45 and Melan A expression and age, diameter, and multicentricity (*p* = 0.64, *p* = 0.55, *p* = 0.85 respectively for HMB45) (*p* = 0.93, *p* = 0.71, *p* = 0.85 respectively for Melan A).

## Discussion

The most important prognostic parameter in thyroid medullary carcinomas is the stage at the time of diagnosis. Certain rare subtypes and differentiations in MTCs are considered to be able to affect the prognosis independent from the stage. Morphological, immunohistochemical and molecular methods can be used to investigate these features. We investigated the presence of melanocytic differentiation that was reflected or not reflected in the morphology in MTCs together with the relationship between the melanocytic differentiation and prognostic markers, a subject that has not been clearly evaluated in the literature previously.

The versatile differentiation of tumor cells in medullary carcinoma is rarely reported. Melanocytic differentiation can be seen as accumulation of melanin in the tumor cell cytoplasm and stroma [2–4,8–11]. Intense dark brown pigment accumulation was noticed in the cytoplasmic and intracellular area on histopathological examination in one of our cases. This case

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