IMP3 Expression in Thyroid Cancers and its Relationship with Prognostic Parameters

Gamze Özcan¹, Mihriban Gürbüzel, MD²* and Serap Pamak Bulut, MD³

¹Pathology Department, Mehmet Akif Ersoy State Hospital, Türkiye
²Pathology Department, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Türkiye
³University of Health Sciences Hamidiye Vocational School of Health Services, Türkiye

*Corresponding author: Mihriban Gürbüzel, MD, PhD Candidate, Pathology Department, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul, Türkiye, Tel: +90-505-4987207, Fax: +90-216-606-33-95

Summary

Objective: To determine the expression of IMP3 (Insulin-like growth factor-II mRNA binding protein 3), which has been reported to be associated with poor prognosis in many organ malignancies, in thyroid malignant tumors and to determine its relationship with prognostic factors such as age, gender, tumor size, and histological type of tumor.

Materials and methods: The study included 60 cases diagnosed with thyroid carcinoma in the pathology department of Haseki Hospital. As the control group, two follicular adenomas, three Hurthle cell adenomas, and five nodular hyperplasia cases were included in the study. Immunohistochemistry was performed using the IMP3 polyclonal antibody.

Results: 50 cases were diagnosed with papillary thyroid carcinoma, five cases with medullary carcinoma, one case with anaplastic carcinoma, and four cases with well-differentiated tumors with uncertain malignant potential. When IMP3 staining results were evaluated, 48 (80%) of 60 thyroid carcinoma cases had positive staining with IMP3. Of the 48 cases with positive staining, 26 (43.3%) had 1+, 16 (26.7%) 2+, 6 (10%) 3+ stainings. Positive staining was present in 7 (70%) cases in the control group. No 3+ staining cases were detected in the control group.

Conclusion: When the prognostic parameters were evaluated, no statistically significant correlation was found between IMP3 expression and age, gender, tumor size, tumor histological type, vessel invasion, lymph node metastasis, multifocality/multicentricity. All of the cases whose IMP3 expression was evaluated as 3+ were papillary thyroid carcinoma.

Keywords
Thyroid carcinoma, IMP3, Prognosis

Introduction

Thyroid carcinomas constitute 1% of all carcinomas in the world and are the most common malignancy of the endocrine system [1]. Due to the similarities between benign and malignant thyroid lesions and the subjective criteria, there may be differences in the evaluation between pathologists. Although immunohistochemistry markers such as HBME-1, Galectin-3, CEA, calcitonin, thyroglobulin, and TTF-1 are currently used to support the diagnosis, the need for ideal markers still continues [1-4]. IMP3 (Insulin-like growth factor-II mRNA binding protein 3) affects cell proliferation by regulating the transcription of insulin-like growth factor-II and plays an important role in RNA stabilization, cell growth, and migration during embryogenesis [5-7]. While Imp3 expression is not expected in normal tissues, it has been positively detected in malignant tumors of organs such as the colon and bladder [7]. It is associated with a poor prognosis in many organ malignancies, and IMP3 expression is high in metastases [8,9]. Our aim with this study is to determine the expression of IMP3 in benign and malignant thyroid tumors diagnosed in our clinic and to determine its relationship with prognostic factors such as age, gender, tumor size, histological type of tumor, vessel invasion, thyroid capsule invasion, surgical margin involvement, and lymph node metastasis.

Materials and Methods

Two pathologists evaluated 464 cases who underwent thyroidectomy or lobectomy in the pathology...
department of Haseki Training and Research Hospital between January 2011 and June 2012, and 60 cases diagnosed with thyroid carcinoma were included in the study. Hematoxylin-Eosin (HE) stained preparations of the patients included in the study were retrospectively analyzed and re-evaluated for histological type and histological subtype, thyroid tissue around the tumor, tumor capsule invasion, vessel invasion, thyroid capsule invasion, surgical margin, soft tissue invasion around the thyroid, perineural invasion, presence of calcification and necrosis. The cases were divided into two groups according to age as ≤ 45 and > 45. According to tumor size, the cases were divided into three groups as ≤ 1 cm, 1-4 cm and > 4 cm. Tumors were examined under 4 main groups according to their histological type: Papillary carcinoma, medullary carcinoma, anaplastic carcinoma, and well-differentiated tumor with uncertain malignant potential. Papillary carcinoma was divided into six groups according to histological subtype as classical type, follicular type, microcarcinoma, macrofollicular type, Warthin-like type and oncocytic type.

IMP3 polyclonal antibody (dilution: 1/100, rabbit polyclonal antibody, Code: GTX115459, Lot No. 40674, Genetex, USA) was used for immunohistochemical staining. Immunohistochemical staining was performed in a humidified, wet environment with a temperature up to 24 °C. As a result of immunohistochemical staining, cytoplasmic expressions of IMP3 were evaluated in the study and control groups. When evaluating the staining intensity; 0 negative; 1+ as weak positive; 2+ as moderately strong positive and 3+ was rated as highly strong positive.

Statistical analysis

Statistical analysis of the obtained data was performed by using SPSS 16.0. Data in the study were presented as mean value and percentage. Prognostic parameters and expression of IMP3 were compared using chi-square test, One-Way ANOVA test and Independent T-test.

Results

The mean age of 60 thyroid carcinoma patients included in the study was 47.65 ± 13.64 years. There were 26 (43.3%) cases aged 45 years and younger, and 34 (56.7%) cases over 45 years of age. 14 (23.3%) of the cases were male and 46 (76.7%) were female. When the cases were grouped according to histopathological type, 50 cases (71.4%) diagnosed with papillary thyroid carcinoma, 5 cases (7.1%) diagnosed with medullary carcinoma, 1 case diagnosed with anaplastic carcinoma (1.4%), 4 cases diagnosed with well-differentiated tumor with uncertain malignant potential (5.7%) were in the study. In the control group, there were 2 cases (2.9%) diagnosed with follicular adenoma, 3 cases (4.3%) diagnosed with Hurthle cell adenoma, and 5 cases (7.1%) diagnosed with nodular hyperplasia. Among the
staining was observed in 7 (70%) cases in the control group, and 4 (40%) were evaluated as 1+ and 3 (30%) as 2+. There were no detected 3+ staining cases in the control group and no staining was observed in 3 (30%) cases.

While there was 1+ staining in 7 (46.7%) and 2+ staining in 4 (26.7%) of 15 cases with tumor size ≤ 1 cm, no staining was observed in 4 (26.7%) of these. Out of 34 cases with tumor diameter between 1 and 4 cm, 15 (44.1%) staining was 1+, 9 (26.5%) 2+ and 5 (14.7%) 3+ staining. No staining was observed in 5 of these patients with tumor size between 1 and 4 cm. Of 11 cases with tumor diameter > 4 cm, 4 (36.4%) staining was 1+, 3 (27.3%) 2+, 1 (9.1%) 3+ staining, 3 (27%), 3) no staining was observed in the case. There was no significant difference in terms of IMP3 staining score between cases with tumor diameters of ≤ 1 cm, 1 cm to 4 cm, and > 4 cm (p > 0.05). There was no significant difference in terms of IMP3 staining score according to gender between the cases aged ≤ 45 and > 45 years (p > 0.05). In the study group, 21 (42%) of 50 cases diagnosed with papillary carcinoma were 1+, 14 (28%) 2+, 6 (12%) 3+, while no staining was observed in 9 (18%) cases. While 1+ staining was observed in 3 (60%) of 5 cases diagnosed with medullary carcinoma, staining was not observed in 2 (40%). In cases diagnosed with medullary carcinoma, 2+ and 3+ staining was not observed with IMP3. 2+ staining was observed in one case in the study group diagnosed with anaplastic carcinoma. While it was 1+ in 2 (50%) and 2+ in 1 (25%) of 4 patients diagnosed with Well Differentiated Tumor with Uncertain Malignant Potential (WDTUMP), staining was not observed in 1 (25%) patient.

When 50 patients diagnosed with papillary carcinoma were evaluated according to carcinoma subtypes, 5 (38.5%) of 13 patients diagnosed with classical papillary carcinoma were 1+, 3 (23.1%) were 2+, 2 (While there was 3+ staining in 15.4% and no staining was observed in 3 (23.1%) cases. Of 17 cases diagnosed as follicular type papillary carcinoma, 9 (52.9%) had 1+ staining, 4 (23.5%) had 2+ staining, 2(11.8%) had 3+ staining, and no staining was observed in 2 (11.8%) case.

1+ staining was observed in 1 (33.3%) of 3 cases diagnosed with Warthin-like type papillary carcinoma, and 2+ staining was observed in 2 (66.7%) cases. While 1 (33.3%) of 3 cases diagnosed with oncocyic papillary carcinoma had 1+ staining, 2 (66.7%) had 3+ staining, and there were no cases that were not stained with IMP3 and stained 2+. 2+ staining was observed in the only macrofollicular type papillary carcinoma case in the study group. There was no significant difference between papillary carcinoma subtypes in terms of IMP3 staining score (p > 0.05) (Table 1 and Table 2).

Due to the very high p value, grouping was made between histological types and the results are given in Table 1.

### Discussion

Thyroid carcinomas constitute 1% of all cancers in the world and it is estimated that there are 122,000 new cases of thyroid carcinoma each year. 5-year survival is

---

**Table 1:** Comparison of papillary carcinoma and other carcinoma types with IMP3 staining percentages.

<table>
<thead>
<tr>
<th>Carcinoma Type</th>
<th>IMP3 expression</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary Carcinoma (50 cases)</td>
<td>Negative 9 (18%)</td>
<td>1+ 21 (42%)</td>
</tr>
<tr>
<td></td>
<td>p = 0.160</td>
<td></td>
</tr>
<tr>
<td>Other types of carcinoma* (10 cases)</td>
<td>3 (30%)</td>
<td>5 (50%)</td>
</tr>
</tbody>
</table>

*Other types of carcinomas: WDTUMP (Well-Differentiated Tumor of Uncertain Malignant Potential), Medullary Carcinoma, Anaplastic Carcinoma.

**Table 2:** Relationship between prognostic parameters and IMP3 expression.

<table>
<thead>
<tr>
<th>Prognostic parameters</th>
<th>IMP3 expression</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 45 (n = 26)</td>
<td>6 (23.1%)</td>
<td>15 (57.7%)</td>
</tr>
<tr>
<td>&gt; 45 (n = 34)</td>
<td>6 (17.6%)</td>
<td>11 (32.4%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 46)</td>
<td>6 (13.1%)</td>
<td>22 (47.8%)</td>
</tr>
<tr>
<td>Male (n = 14)</td>
<td>6 (42.9%)</td>
<td>4 (28.6%)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1-4 cm (n = 34)</td>
<td>5 (14.7%)</td>
<td>15 (44.1%)</td>
</tr>
<tr>
<td>&gt; 4 cm (n = 11)</td>
<td>3 (27.3%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Histological subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma (n = 50)</td>
<td>9 (18.0%)</td>
<td>21 (42.0%)</td>
</tr>
<tr>
<td>Medullary carcinoma (n = 5)</td>
<td>2 (40.0%)</td>
<td>3 (60.0%)</td>
</tr>
<tr>
<td>Anaplastic carcinoma (n = 1)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>WDTUMP (n = 4)</td>
<td>1 (25.0%)</td>
<td>2 (50.0%)</td>
</tr>
</tbody>
</table>
around 90% [1]. IMP3 is an oncofetal protein and belongs to the IGF-II mRNA binding protein family like IMP1 and IMP2 [10]. Members of the IMP family are implicated in RNA movement and stabilization, cell growth, and cell migration in the early stages of embryogenesis [6,7]. The IMP3 gene is located on chromosome 7p11.2 [11]. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growing epithelium, muscle and placenta during human and mouse embryogenesis. It is reported that it is produced too little to be detected in placenta during human and mouse embryogenesis. It is a protein equivalent to KOC (K homologous domain-containing protein over expressed in cancer) protein that clones from pancreatic tumors [12]. IMP3 is secreted from the growth
Histological type of tumor is one of the most important prognostic parameters that affects survival. Although the 10-year survival rate is over 90% in well-differentiated thyroid carcinomas except medullary carcinoma, it is known that follicular carcinomas have a more aggressive course. In anaplastic carcinomas, the 10-year survival rate is extremely low \[20,21\]. Mortality risk was found to be higher in follicular carcinomas compared to papillary carcinomas \[20\]. In a study, it was reported that 82.1% of malignant thyroid tumors were positive with IMP3. Again, according to this study, no significant difference was observed between benign and malignant tumors \[22\].

When the prognostic parameters were evaluated, vascular invasion was found in 18% of papillary carcinomas (9 cases), 60% of medullary carcinomas (3 cases) and 100% of anaplastic carcinomas (1 case), and that was found a statistically significant (p = 0.024). Lymph node metastases were present in 10% of papillary carcinomas, 40% of medullary carcinomas, and 100% of anaplastic carcinomas, and these findings also were statistically significant (p = 0.014).

Multicentricity causes an increase in local recurrence and mortality, especially in papillary carcinoma \[23\]. In a study conducted with 700 thyroid carcinomas, it was reported that tumor recurrence was 1.7 times higher in multifocal tumors than unifocal tumors, but no correlation was found between multifocality and mortality \[19\]. In our study, multifocality/multicentricity was detected in 23 (38.3%) cases, but not in 37 (61.7%) cases. Of the cases with multifocality/multicentricity, 20 (87%) were papillary carcinoma, 2 (8.7%) medullary carcinoma, 1 (4.3%) anaplastic carcinoma. This finding was consistent with the literature.

As a result; It has been shown that IMP-3 plays a role in carcinogenesis and prognosis in many malignant tumors including hepatobiliary system, esophagus, stomach, pancreas, urothelial tumors and melanocytic lesions. There are few studies indicating that IMP-3 is useful in the differentiation of follicular tumors in thyroid carcinomas and that it can be an effective parameter in determining the prognosis in thyroid carcinomas with an aggressive course. According to our study, all of the cases whose IMP3 expression was evaluated as 3+ were papillary thyroid carcinoma. However the findings of our study show that IMP3 expression does not fully differentiate between thyroid carcinoma types and is not effective as a prognostic indicator. These findings show that more studies should be done in large series to determine the status of IMP3 expression in thyroid carcinoma cases and its importance in the prognosis, as it is not compatible with the small number of literature.

**Author’s Contributions**

MG and GÖ conceived and designed the study. MG, GÖ, SPB supervised the conduct of the study and data collection. MG, GÖ and SPB managed the data, including quality control. GÖ and MG analyzed the data. GÖ, MG, SPB performed the literature review. MG and GÖ drafted the article, and all authors contributed substantially to its revision. MG takes responsibility for the paper as a whole.

**Statement Conflict of Interest**

No conflict of interest was declared by the authors.

**References**


