Statistical Analysis of Histomorphological Findings in Medullary Thyroid Carcinoma: Distinction Between the Different Familial Forms of the Disease

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Statistical Analysis of Histomorphological Findings in Medullary Thyroid Carcinoma: Distinction Between the Different Familial Forms of the Disease


A multifactorial analysis of morphological findings was performed on 153 cases of medullary thyroid carcinoma (MTC). The aim of the study was to utilize histological criteria to discriminate between MTC associated with multiple endocrine neoplasia type 2A (MEN 2A) and that associated with the inherited MTC only syndrome. The presence of fusiform cells associated with several other markers seemed to be more predictive of MEN 2A. A comparison of inherited MTC only and sporadic MTC showed fusiform cells to be significantly less common in inherited MTC only. These results suggest that the inherited MTC only syndrome is a distinct clinical and morphological entity. Further investigations are needed to confirm the finding and understand its implications. (Henry Ford Hosp Med J 1992;40:261-3)

In a previous study (1), we analyzed the pathological features of 153 cases of medullary thyroid carcinoma (MTC) excluding from analysis 11 cases of multiple endocrine neoplasia type 2B (MEN 2B). The purpose of the study was to discriminate between the different forms of the disease. The results of multifactorial analysis showed that bilaterality by itself permitted a correct classification of 93% of the familial forms when compared with sporadic disease. We were less successful, however, in distinguishing between familial isolated MTC and familial MTC associated with MEN 2A. To try to improve our identification and classification of tumors, we performed a more detailed analysis.

Materials and Methods

The 153 patients (68 males and 85 females) reported in the Table constituted the study population. Patients diagnosed solely on the basis of clinical features before any family investigation were termed index cases. All sporadic cases belong to this group, and among them, four cases of MEN 2A (Table). The 77 familial cases were derived from 33 families (in these families, data were available for 1 to 8 cases, not always including index cases).

Histological samples were collected in France by members of the Groupe d'Etude des Tumeurs a Calcitonine (GETC) and reviewed by a group of 13 pathologists. For each group, 51 separate features were analyzed including sex; age; associated disease; follow-up pathological findings, such as macroscopic aspects (unilaterality or bilaterality, uninodular or multinodular tumor, size in each lobe); microscopic aspects (with reference on stroma, amyloid content, patterns, cells, C-cell hyperplasia); other thyroid disease; and immunostaining for calcitonin, carcinoembryonic antigen, and thyroglobulin. Univariate analyses (chi-square, Student t test) and multifactorial analyses (discriminant analyses, logistic regression) were performed.

Results

A more detailed analysis allowed us to readdress the question of determining discriminating parameters between familial isolated MTC and familial MEN 2A. Three-fourths (78%) of the cases were correctly classified. As previously observed (1), the presence of fusiform cells, associated with one or two other markers seemed to be the most predictive factor for discrimination between the two types of tumor. Two different patterns were observed. In MEN 2A, 78.2% (44 of 56) had fusiform cells without a follicular pattern (Fig 1) whereas the remaining 12...
Table
Description of Patient Samples

<table>
<thead>
<tr>
<th>Sporadic Cases: 76</th>
<th>Familial Cases: 77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated MTC: 72</td>
<td>Isolated MTC: 21</td>
</tr>
<tr>
<td>MEN 2A: 4</td>
<td>MEN 2A: 56</td>
</tr>
<tr>
<td>12 kindreds</td>
<td>21 kindreds</td>
</tr>
<tr>
<td>10 index cases</td>
<td>16 index cases</td>
</tr>
</tbody>
</table>

cases could not be classified. In contrast, 76.2% (16 of 21) of the familial MTC tumors had a follicular pattern without fusiform cells (Fig 2) with 5 of 21 unclassifiable.

Index cases could not be classified with exactly the same parameters. The presence of fusiform cells in the tumors without oxyphilic aspects of the tumor cells permitted the correct classification of 81% (13 of 16) of the MEN 2A cases. The absence of fusiform cells and the presence of oxyphilic cells (Fig 3) permitted us to correctly classify 80% (8 of 10) of the familial isolated MTC.

One possible explanation for our failure to classify a higher percentage of MEN 2A tumors is the variability of expression of the features of MEN 2A (MTC plus pheochromocytoma and/or hyperparathyroidism). It is of interest that the MEN 2A cases which could not be correctly classified belong to kindreds in which the expression of the disease is variable. On the other hand, familial MTC cases which could not be correctly classified belong to only two families. We cannot exclude the possibility that members of those families may later express other MEN 2A features.

Discussion

It is not possible to use these results in a practical clinical way to determine the type of MTC in any individual case. They are useful preliminary data for further investigations and to encourage new concepts. What does the presence of fusiform cells mean? Does their presence provide a marker to distinguish between familial isolated MTC and MEN 2A?

A discriminant analysis between familial isolated MTC and sporadic MTC permitted confirmation of the known discriminant factors such as bilaterality and C-cell hyperplasia (2,3). A univariate analysis confirmed (P < 0.03) that fusiform cells are more common in sporadic MTC than in the familial MTC only syndrome.

These results lead to additional questions. Are these results merely a pathological curiosity or an important event in the natural history of MTC? Is familial MTC only (4) a special kind of MTC from a histogenetic point of view? Could these tumors be an alteration in the differentiation of the C-cell or an associated mutation of the endodermic part able to express endocrine peptide differentiation of the ultimobranchial body (5-8)?
Acknowledgments

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References