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Immunohistochemistry in Medullary Thyroid Carcinoma: Prognosis and Distinction Between Hereditary and Sporadic Tumors

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In this retrospective study of 68 cases of medullary thyroid carcinoma (MTC), morphological features were studied, which could be helpful in prognosis and in the distinction between hereditary and sporadic forms of the disease. Necrosis within the tumors seemed to carry a poor prognosis. Bilateral MTC, unquestionable C-cell hyperplasia, glandular or follicular pattern, and thyroglobulin-positive cells seemed to be more prevalent in hereditary forms of the disease. A smaller proportion of calcitonin-immunoreactive cells were encountered in hereditary tumors than in sporadic tumors. (Henry Ford Hosp Med J 1987;35:139-42)

Thirteen hereditary cancers and 55 probably sporadic cancers were reviewed by ten histopathologists. The diagnostic value of immunohistochemistry was evaluated using calcitonin (CT) and carcinoembryonic antigen (CEA) to distinguish tumor emboli from C-cell hyperplasia and/or to detect a more circumscribed C-cell hyperplasia. Thyroglobulin (Tg) was used to detect the mixed form of medullary thyroid carcinoma (MTC).

Five parameters seemed to be predictive of the diagnosis of the hereditary form: bilaterality, C-cell hyperplasia, mixed histological forms, Tg-positive cells, and a CT-cell positivity index of less than 50%. The only factor indicative of a poor prognosis was necrosis within the tumors.

Materials and Methods

Patients

Sixty-eight cases from 14 different institutions were reviewed by the group of pathologists associated with Groupe d'Etude des Tumeurs a Calcitonine. Unfortunately, some cases lacked information regarding the relationship of the tumor to the thyroid capsule and/or the presence of extra thyroidal involvement. The disease was staged clinicopathologically as shown in the Table.

Histopathologic examination

All microscopic slides were examined by each of the ten members of the group; none of the pathologists had knowledge of the clinical data. The slides were stained with hematoxylin-eosin, periodic acid-Schiff, alcian blue, grimelius, and Congo red. Immunoperoxidase studies using anti-CT, anti-CEA, and anti-Tg were performed. Stroma, amyloidosis, and necrosis were quantified. Architectural patterns were noted including follicles, cytologic features, mitotic index, cellular atypia, and vascular embolism. The number of immunoreactive CT, CEA, and Tg cells was ascertained, and the immunoreactivity was expressed in percentage of positively stained cells (< 25%, 25% to 50%, 50% to 75%, > 75%).

Results

Incidence

Twelve patients were accepted to have the sporadic form of the disease, one of whom had multiple endocrine neoplasia type 2B (MEN-2B). Thirteen patients from six different families (19.1%) had a positive family history ascertained to be MEN-2A in five individuals and isolated MTC in five individuals. It was not ascertained whether the case was hereditary or sporadic in 43 individuals. The mean age at diagnosis was 33 years for the hereditary cases and 46 years for the other cases.

Table
Clinicopathological Staging

	Stage*			
	?	1	2	3
Number of Cases	6	42	19	1
Males	1	13	9	1
Females	5	28	9	0
Sporadic	6	32	16	1
Hereditary				
Isolated MTC	0	5	0	
MEN-2A	0	3	2	
Unknown	0	2	1	

*Stage ? = macroscopic detail lacking. Stage 1 = tumor localized to the thyroid gland. Stage 2 = direct local invasion or fixed cervical lymph nodes. Stage 3 = distant metastases.

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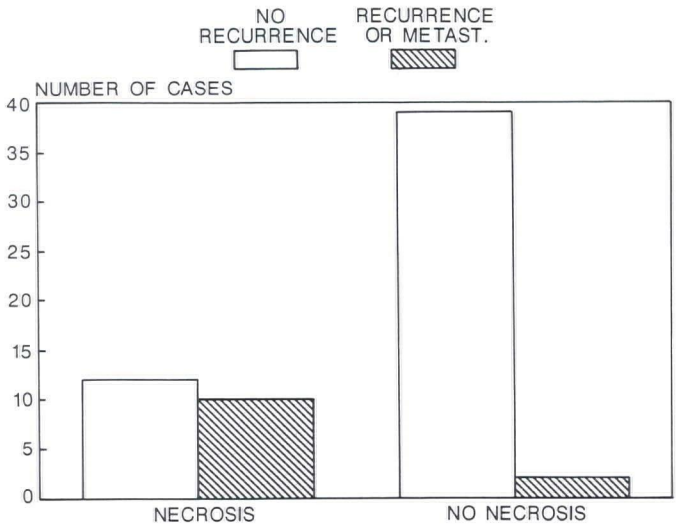

Fig 1—Microscopic appearance.

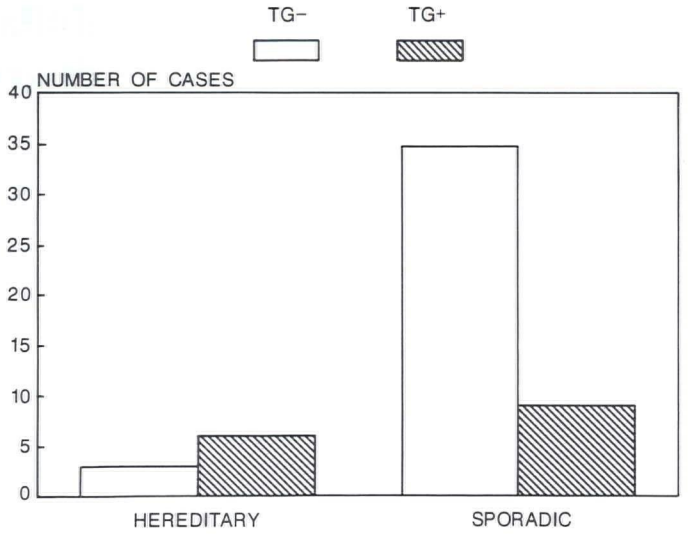

Fig 3—Tumor thyroglobulin.

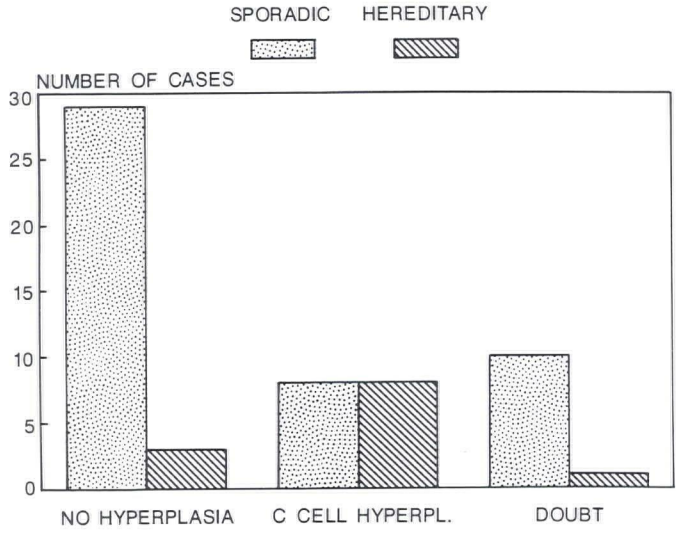

Fig 2—C-cell hyperplasia, hereditary or sporadic.

Clinical features

Follow-up duration varied from one year to more than ten years, with two patients followed for at least 15 years. Eleven cases (16%) constituted the poor prognosis group with known recurrences and metastases, with four cases ending fatally.

Pathologic features

The pathologic features reviewed were similar to those reported previously (1-4).

C-cell hyperplasia—The presence of C-cell hyperplasia was unquestionable at times, but in many instances was difficult to assess because it could not be distinguished from tumor extension or vascular embolization. CT staining was helpful at times, although at times it was impossible to ascertain the presence or absence of C-cell hyperplasia.

Follicular pattern—Tg-positivity—A follicular pattern with or without colloid-like material was ascertained, although some patterns were indistinguishable from normal follicles. Tg-positivity led us to distinguish three possibilities: 1) follicular pattern, Tg positive; 2) follicular pattern, Tg negative; and 3) no glandular or follicular pattern, with Tg-positive cells scattered throughout the tumor.

Prognostic factors

Our crude statistical analysis showed significant correlation between clinical staging and prognosis ($P < 0.05$), necrosis and prognosis ($P < 0.01$) (Fig 1), and necrosis and clinical staging ($P < 0.02$). No significant correlation was found between prognosis and the extent of thyroid involvement, architectural patterns, amyloidosis, mitotic figures, vascular embolism, or CT, CEA, and Tg staining. Variation in nuclear size could possibly be considered as a poor prognostic sign ($P < 0.1$).

Discrimination between hereditary and sporadic forms of the disease

Bilaterality—Bilaterality was a highly significant discriminant criterium present in all of our hereditary cases (except one in whom available information was inadequate) ($P < 0.0002$).

C-cell hyperplasia—The presence of C-cell hyperplasia was a highly significant factor ($P < 0.01$), if the doubtful group is excluded (Fig 2).

Follicular patterns—The presence of follicular or glandular patterns seemed to be highly discriminant for the hereditary type ($P < 0.01$).

Tg-positivity—Tg-positivity was not always correlated with glandular or follicular patterns, but appeared to be more common in the hereditary type ($P < 0.02$) (Fig 3).

CT-cells staining positivity index—Interestingly, less than 50% of the cells were CT-positive more often in hereditary tumors than in sporadic tumors ($P < 0.02$).

Discussion

Diagnostic factors

Our data agree with others' in that the stage of the disease at presentation is the major prognostic factor (1,2). Patients with direct extension did not have a significantly better survival rate than those with distant metastases, which confirms the data of Saad et al (1) and Russell et al (5).

The prognostic significance of necrosis is not generally appreciated, although necrosis has been mentioned as a prognostic factor in older series (6,7). Necrosis seemed to be a highly significant prognostic factor which correlated with the clinical staging.

Our studies did not confirm recent data (1,8) regarding the prognostic value of tumor markers. We did not find a correlation between the course of the disease and the degree of CT staining.

Discrimination between hereditary and sporadic variety of the disease

In agreement with the literature (1,5,9), all our hereditary patients had bilateral MTC. However, nine of the tumors from patients with "sporadic" disease were bilateral, but this group included a large number of cases with incomplete data as to whether or not they were truly sporadic cases. Even though bilaterality has been observed in sporadic forms (1,5), we believe that the families of these cases should be studied carefully for the hereditary disease.

Wolfe et al (10) demonstrated in 1973 that the earliest pathologic change in hereditary MTC was a progressive multifocal increase in the number of C-cells in the middle thirds of the lateral lobes of the thyroid. In 1979, Carney et al (11) described a study of C-cell disease of the thyroid gland in MEN-2B: "The earliest abnormalities were hypertrophy and proliferation of C-cells confined within the basement membrane of the follicle. Located in the thyroid parenchyma adjacent to, but beyond, the obvious tumor margin were individual cells or small clusters of abnormal C-cells in a parafollicular or intrafollicular location." In 1983, Emmertsen et al (12) showed that the presence of C-cell hyperplasia together with MTC could serve as a histopathologic marker for the hereditary variety of the disease. On the other hand, Ulbright et al (13) in 1981 described C-cell hyperplasia developing in residual thyroid following resection for sporadic medullary carcinoma. In 1981, Howieson Gibson et al (14) found C-cell nodules in adult human thyroid at autopsy. They suggested that C-cell clusters may be fairly common in a normocalcemic geriatric population (autopsy cases studied were on patients older than 50 years of age). In 1985, O'Toole et al (15), in studying effect of age on the number of CT-immunoreactive cells in the thyroid gland, demonstrated that the CT-immunoreactive cells tended to aggregate in clusters in a pattern similar to that seen in C-cell nodules in older persons. These reports emphasize some of the difficulties in utilizing C-cell hyperplasia to discriminate between hereditary and sporadic forms of MTC.

It is well known that follicular and tubular patterns occur in MTC (4,16,17). Furthermore, several cases exhibiting these patterns were reported (17-20). Ljungberg et al (18) proposed a distinct pathologic entity consisting of tumors formed of both follicular and C-cell elements, which they called differentiated thyroid carcinoma: the intermediate type. In 1982, Hales et al (17) reported MTC with immunoreactivity for both calcitonin and thyroglobulin, as has been reported subsequently by others (4,20). Tg-positivity is not present in glandular or follicular structures only. Holm et al (21) in 1986 demonstrated the concurrent production of Tg and CT by the same neoplastic cells. Holm et al (20), in a 1985 review of 27 cases of MTC, suggested that patients with Tg-producing tumors were generally younger than those with the non-Tg-producing tumors. No morphologic features by light or electron microscopy were noted which permitted Tg-positive MTC to be differentiated from the more "common" type of MTC without Tg-positivity.

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