Light and Electron Microscopical Study of C cells in Thyroid Diseases

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INTRODUCTION
The presence of a distinct system of parafollicular cells in the thyroid gland was first described by Nonidez in 1932. They comprise 0.1% of the mass of the adult normal human thyroid [1] and they have the ability to synthesize and store catecholamines or indolethylenamines after uptaking and decarboxylating the precursors of these substances (APUD).

C cells show positive immunoreactivity for calcitonin, chromogranin, low molecular weight keratins, calcitonin gene-related peptide and CEA, but not for thyroglobulin [2]. The aim of our study was to evaluate C-cell morphology and their possible alterations in the tissue adjacent to benign and malignant thyroid lesions.

MATERIALS AND METHODS
We studied 44 patients, mainly women (33), aged from 30 to 65 years, surgically treated in our hospital for different thyroid lesions. The microscopical diagnosis revealed 19 cases of nodular or adenomatoid goitre and 25 cases of carcinomas, which comprised five cases of follicular carcinoma, 14 of papillary carcinoma and six of anaplastic carcinoma. Entire lobes of some specimens were stained with haematoxylin and eosin (H&E) and immunohistochemistry (chromogranin stain).

Tissues for the transmission electron microscopy were taken from the normal thyroid tissue adjacent to follicular-cell derived benign and malignant lesions. These specimens may be fixed in 3% glutaraldehyde, post-fixed in 2% osmium tetroxide, stained in 1% uranyl acetate and embedded in Epon. Thin sections were stained with lead citrate and examined in a JEOL TEM 2000 FX II.

RESULTS
On routine haematoxylin and eosin staining the parafollicular cells appeared polygonal, larger than follicular cells and contained a pale-staining granular cytoplasm and central or eccentric oval nuclei (Fig 1). However, since their recognition was very difficult in most cases, we used the chromogranin stain which identified the secretory granules and thus disclosed these cells (Fig 2). The C cells were evident in the normal-appearing parenchyma adjacent to thyroid nodules but we did not observe them within the adenomatoid nodules or carcinomas of follicular-cell origin in any cases.

Ultrastructurally, in most benign cases we observed that the parafollicular cells had their normal architectural structure and occupied an interfollicular localization, being separated from the interstitium by the follicular basal lamina and from the luminal colloid by extensions of the follicular cell cytoplasm. In other cases, they were in groups of two or three cells in the interfollicular stroma. The basal lamina was focally thickened (Fig 3).

A characteristic finding was the relative diminution of the C-cell cytoplasmic dense granules. These granules were of unequal size. Some were very small with a round shape, usually isolated in small clusters of 2-3, delineated...
by a cell membrane, with osmiophilic material in the centre and a clear thin zone external. Others, usually found in clusters, were of larger size, with an oval or slightly elongated shape (Fig 4).

Certain cells contained fat droplets within their cytoplasm. On the other hand, in the malignant cases we observed a marked alteration of the parafollicular architectural structure, with the appearance of amorphous material and abundant connective tissue, with newly formed capillary vessels within it (Fig 5). The C cells were scattered or in clusters, with normal nuclei, dilated rough endoplasmic reticulum, as well as an adequate number of polyribosomes, some fat droplets, microfilaments, vesicles and very few (1-3) granules bounded by a cell membrane (Fig 6). In the 12 out of 25 malignant cases (48%) which concerned two follicular carcinomas, seven papillary carcinoma and three anaplastic carcinoma, there was an increase in the number of the C cells, as seen with at least three low power (x100) fields per slide, each containing more than 50 C cells, and some follicles lined entirely by C cells.

In a few cases, the C-cell hyperplasia was of a nodular type, with a complete obliteration of follicular space by C cells and the production of solid intrafollicular aggregates. This finding was also observed in two cases of adenomatoid nodules. So, C-cell hyperplasia was observed in 14 out of 44 cases (34%).

**DISCUSSION**

According to the literature, many investigators have already studied thyroid C cells, both in normal subjects and in patients with multiple endocrine neoplasia syndrome (MENS) [3-6]. As far as we know there are no studies, using electron microscopy, on C cells in diseases of the follicular epithelium of the thyroid gland and there are few optical microscopy studies addressing the same issue [7,8].

Livolsi et al. [9] examined the C cells in normal thyroid tissue adjacent to four cases of papillary carcinoma, three follicular adenomas, 13 cases of nontoxic nodular goitre and four cases of Hashimoto's thyroiditis and found no evidence of C-cell hyperplasia. But the small number of tumours included in this study may explain the negative results.

On the other hand, Scopsi et al. [10] observed diffuse and nodular C-cell hyperplasia in 30% of their cases, which concerned thyroid diseases other than medullary carcinoma.

Moreover, Albores-Saavedra et al. [11] reported a statistically significant increase in the number of C cells in the normal-appearing thyroid tissue adjacent to follicular cell tumours (34.6% of the cases), a finding which was in agreement with our results. The explanation for the association of C-cell hyperplasia with follicular and papillary carcinoma is unknown. Albores-Saavedra et al. [11] speculate that thyroid tumours induce a reactive or compensatory type of C-cell hyperplasia. Hyperplasia of neuroendocrine cells [12] has also been demonstrated in response to a variety of non-specific, chronic stimuli in many other organs including the lung, small and large intestine, gallbladder, stomach, urinary bladder and skin. Another possible explanation is that the destruction of thyroid parenchyma (including the C cells) by the tumour leads to chronic TSH overstimulation and C-cell hyperplasia. Several investigators [13] suggested that TSH stimulates both follicular and C cells.

The significance of C-cell hyperplasia is also unknown [8,11]. However, it is clear that some cases of symptomatic C-cell hyperplasia due to elevated serum calcitonin levels, which were associated with follicular cell tumours, may be a source of diagnostic error and should be considered in the pre-operative differential diagnosis of medullary carcinoma.

The neoplastic potential of the C-cell hyperplasia could be a possible explanation for the rare cases of papillary carcinoma and medullary carcinoma coexisting in the same thyroid gland [14]. It is worth saying that in our study we found C-cell hyperplasia in 48% (12 out of 25) of our malignant cases, while this finding has been observed in 10.5% (2 out of 19) of our non-neoplastic (benign) cases. According to our knowledge, this association has not previously been described. However, Guyetant et al [15] in their research on C-cell hyperplasia in correlation with chronic lymphocytic thyroiditis reported that its frequency was higher if a follicular cell tumour was associated with chronic lymphocytic thyroiditis, while Derizhanova and Sidorenko [16]...
in their study observed that C-cell hyperplasia was the backdrop for each form of thyroid cancer and increased as tumour-cell differentiation decreased.

Finally, it seems that the alterations in the number or the morphology of C cells, although not conclusive, can offer some advantages in the diagnostic evaluation of thyroid lesions.

REFERENCES


