An encapsulated oncocytic neoplasm of follicular origin of thyroid, expressing neuroendocrine markers. A case report and literature review

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Summary
A case is reported of an oncocytic tumor of the thyroid expressing simultaneously follicular and neuroendocrine markers, but not calcitonin. The data reported in the literature and the possible relationships of these lesions with the calcitonin-negative medullary carcinomas were examined.

Key words: thyroid cancer, neuroendocrine markers

Introduction
Thyroid neuroendocrine tumors are classically represented by medullary carcinoma (MTC), which are derived from parafollicular C cells whose immunophenotypic characteristic is to express neuroendocrine markers (synaptophysin, chromogranin, NSE, CD56) and calcitonin. In the literature, however, there are reported cases of thyroid tumors expressing neuroendocrine markers and not calcitonin. A tumor of this type occurred during our observation and forced us to face a somewhat intricate problem, therefore worthy of further study.

Case report
A 74-year-old man had an increase in the volume of the thyroid gland for some months, mainly affecting his left lobe. A fine-needle aspiration performed on him gave a result classified as 3 B. After further sonographic findings, he was subjected to total thyroidectomy.

Materials and methods

MACROSCOPIC EXAMINATION OF THE SURGICAL SPECIMEN
a Right thyroid lobe of 3.5 x 2.7 x 2.5 cm to the section showed a plurinodular aspect;
b left thyroid lobe of 5 x 4 x 3.5 cm to the section showed the glandular parenchyma almost completely replaced by a single capsulated nodule of soft consistency, yellowish color and a central hemorrhagic and saggy area.
The material is fixed in toto in buffered formalin, numerous fragments
Figure 1. (A) Nodule encapsulated at low magnification H.E. (50X); (B, C, D) Solid-trabecular pattern of the neoplastic proliferation, H.E. (120X).

Figure 2. (A, B, C) Cellular elements with oncocytic character. H.E. (250X); (D) Small follicular cavity with a drop of dense colloid. H.E. (250X).
Figure 3. (A) Vimentin (100X); (B) Thyroglobulin (250X); (C) PAX 8 (150X); (D) TTF1 (100X).

Figure 4. (A) Chromogranin (300X); (B) Synaptophysin (250X); (C) CD56 (150X); (D) NSE (250X).
are embedded in paraffin and from them, 5 mm sections are taken, stained with hematoxylin and eosin and subjected to immuno-histochemical investigation with a panel of antibodies: Vimentin, Thyreoglobulin, PAX8, TTF1, Chromogranin A, Synaptophysin, CD56, NSE, Calcitonin.

**Microscopic examination**

The fragment under examination is peripherally delimited by a thick fibrous capsule (Fig. 1A) under which normal-looking thyroid follicles are recognised, compressed by an underlying nodular proliferation. This proliferation, delimited by a thin fibrous capsule, is predominantly solid in appearance and consists of rather large, globose-polyhedral elements with finely granular, acidophilic cytoplasm (Figs. 1B, C). The nucleus is voluminous central. No mitotic activity is found. The elements are organised in trabeculae with little fibrillary stroma interposed (Figs 1D, 2 A-C). Sporadically, abortive follicular formations containing a drop of dense colloid are found (Fig. 2D). Based on the morphological the following diagnosis was made: *Encapsulated oncocytic neoplasm of follicular origin.* The immunohistochemical investigation yielded the results reported in Table I.

**Discussion**

A thyroid neoplasm of follicular origin does not express calcitonin is a known fact. It is also known that some MTC, although rarely, cannot express calcitonin but can still produce calcitonin gene-related peptide (CGRP). It is even rarer that some MTC are negative for calcitonin and CGRP peptides, but contain their corresponding mRNAs \(^1,2,3\) In the short period of time between 1996 and 2001,

**Table I.** Results of the immunohistochemical panel.

| VIM | TG  | PAX8 | TTF1 | CGA  | Syn  | CD56 | NSE  | CT  |
|-----|-----|------|------|------|------|------|------|-----|
|     |     |      |      |      |      |      |      |     |
| Fig 3a | Fig 3b | Fig 3c | Fig 3d | Fig 4a | Fig 4b | Fig 4c | Fig 4d | Figs 5a, b, c, d |

Tg = Thyreoglobulin; CGA = ChromograninA; Syn = Synaptophysin; CT = Calcitonin.
three articles appeared in the literature concerning the expression of neuroendocrine markers by thyroid tumors from follicular cells. 40 thyroid tumors, including the various histotypes of follicular origin, have been tested with NSE, Synaptophysin and chromogranin. 28 tumors (70%) expressed neuroendocrine markers, of which 25% expressed only one, 30% expressed two and 15% expressed three.

In a research conducted on 120 cases of tumors of follicular origin, 36% expressed chromogranin and, in particular, 46.66% of papillaries, 5.5% of follicular and 7% of anaplastic. The positivity ratios between the various histotypes perhaps could be distorted by the fact that 74% of the cases are represented by papillary carcinomas (Tab. II).

A study conducted on 50 cases of thyroid neoplasms relating to the expressiveness of neuroendocrine markers has led to results summarised in the following Table III.

From these studies it would emerge that:

a. the phenomenon of the expression of neuroendocrine markers by the follicular cells of the thyroid gland is a fairly frequent occurrence. Strangely no more recent articles have appeared on the subject, and even more strangely, there is no mention of this phenomenon in the official texts.

b. not all neoplasms of follicular origin express thyroglobulin. This phenomenon is present in all histotypes, and is particularly accentuated in the papillary carcinomas;

c. in the different histotypes NSE, synaptophysin and Leu7 are expressed to varying degrees;

d. with regards to chromogranin, the results reported in the various articles are somewhat uneven. In fact, while in one series the expression of chromogranin is reported in 36% of cases, in another it is not reported in any case.

In summary, the data of the literature, certainly not very abundant, show that not all TMC express calcitonin express thyroglobulin, just as not all tumors of Follicular origin express it. What is certain is that all tumors that express calcitonin are medullary and those that express thyroglobulin are follicular. Between these two extremes, there are different situations such as those relating to TMC with negative calcitonin and Tumors of follicular origin expressing neuroendocrine markers whose frequency is not entirely negligible. A small group of cases of tumors of follicular origin expressing the full spectrum of neuroendocrine markers is reported in Table IV. Despite the non-homogeneity of the data on tumors of

### Table II. Neuroendocrine markers in tumors of follicular origin (from Tseleni-Balafouva et al., 1998, mod.)

| Histology          | N°  | Thyroglobulin | Chromogranin A | Calcitonin |
|-------------------|-----|---------------|-----------------|------------|
| Papillary         | 90  | 99.99%        | 46.66%          | 3%         |
| Follicular        | 18  | 99.99%        | 5.55%           | 0%         |
| Hurtle            | 7   | 99.99%        | 0%              | 0%         |
| Anaplastic        | 7   | 33%           | 16.66%          | 0%         |

### Table III. Neuroendocrine markers in tumors of follicular origin (from Satoh et al., 2001, mod.)

| Histology                | N°cases | NSE     | Syn    | Leu7    | CGA | TG    | CT   |
|--------------------------|---------|---------|--------|---------|-----|-------|------|
| Follicular adenoma       | 11      | 7 (63%) | 5 (45.5%) | 3 (33%) | 0   | 9 (81%) | 0    |
| Follicular carcinoma     | 10      | 9 (90%) | 8 (80%) | 8 (80%) | 0   | 7 (70%) | 0    |
| Papillary carcinoma      | 14      | 12 (85%) | 11 (76.6%) | 14 (100%) | 0   | 8 (57.1%) | 0    |
| Anaplastic carcinoma     | 10      | 1 (10%) | 0      | 0       | 0   | 0     | 0    |
| Medullary carcinoma      | 5       | 5 (100%) | 5 (100%) | 4 (80%) | 5 (100%) | 0 (100%) | 0    |

SYn = Synaptophysin; CgA = Chromogranin A; TG = Thyreoglobulin; CT = Calcitonin.

### Table III. Neuroendocrine markers in tumors of follicular origin (from Parmer et al., 2017, mod.)

| Authors                  | Age/Sex | CT   | CGA | SYN | CEA | TTF1 | TG |
|--------------------------|---------|------|-----|-----|-----|------|----|
| Parmer et al.            | 9       | 74F  | -   | +   | +   | +    | -  |
| Chernyavsky et al.       | 10      | 40F  | -   | +   | NA  | NA   | +  |
| Kim et al.               | 11      | 34M  | -   | +   | +   | -    | +  |
| Kasajima et al.          | 12      | 48F  | -   | +   | +   | +    | NA |
| Mussazhanova et al.      | 13      | 64M  | -   | +   | +   | -    | +  |
| Ismi et al.              | 14      | 57M  | -   | +   | -   | -    | -  |
| Nakazawa et al.          | 15      | 76M  | -   | +   | -   | +    | -  |

CT = Calcitonin; CG = Chromogranin; Syn = Synaptophysin; TG = Thyreoglobulin.
follicular origin expressing neuroendocrine markers, two subsets would seem to be identified, one, more numerous, not expressing chromogranin and another expressing it. The case we observed belongs to the latter category because the tumor, thyroglobulin-positive, expresses all the neuroendocrine markers, including the chromogranin.

**Conclusions**

The study of this case and the literature indicates that the expression of neuroendocrine markers by thyroid neoplasms of follicular origin is not an exceptional event. To date, this phenomenon received little attention from researchers and was often confused with negative calcitonin TMC. This group of follicular tumors expressing chromogranin could represent almost a strained bridge between the two categories of Thyroid tumors whose histogenesis is perhaps less distant than was hitherto considered. Therefore, it is necessary to study more cases to elucidate its implications on a clinical and histogenetic level.

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