**CASE REPORT**

Medico-historical overview and histopathological comments about a hyalinizing trabecular tumor case of thyroid gland

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**Abstract**

Introduction: Hyalinizing Trabecular Tumor (HTT) of the thyroid gland is a rare and controversial tumor, whose rigorous identification is extremely important due to the difficulty of establishing a correct diagnosis using only the routine histological stains (Hematoxylin–Eosin, Periodic Acid–Schiff, van Gieson, etc.). Using only usual stains, difficult problems of differential diagnosis arise. In this paper, we report a clinically unexpected case of HTT, the first in Romania, whose diagnosis has been established only by immunohistochemistry reactions.

Materials, Methods and Results: In assessing a case with nodular goiter for diagnosis purpose, we have found a nodule difficult to diagnose. We have been determined to appeal to some additional immunohistochemical techniques. We present also a medico-historical overview concerning some first descriptions of this rare entity. There are also mentioned some data regarding the behavior of this rare thyroid tumor.

Keywords: thyroid, hyalinizing trabecular tumor, thyroid carcinoma, Ki-67.

**Introduction**

Hyalinizing trabecular tumor (HTT) of the thyroid gland is a rare, unusual and also a controversial neoplasm. This lesion has a short history, as only in 1987 it was put into evidence for the first time by Carney et al. [1]. It is a rare lesion, because after 27 years since it was identified, in the international specialty papers have been communicated less than 100 cases. The HTT is a controversial lesion because, although some authors have considered it as a separate entity [1], other had appreciated it as a variant of sclerozant thyroid carcinoma or a non-specific aspect that may be seen in a variety of thyroid lesions [2–5]. Others, such as Molberg and Albores-Saavedra, suggested that HTT have a malignant counterpart, similar to conventional follicular adenomas, and that papillary thyroid carcinomas may arise within hyalinizing trabecular thyroid tumors [6].

All the authors who have described this lesion showed that it is important to identify correctly HTT, because its diagnosis cannot be established only by routine stains. It is recommended to perform immunohistochemical stains – at least Ki-67 reaction – to correctly identify the HTT. In Romania, immunohistochemical reactions on these lesions have not yet been published.

**Materials and Methods**

A 56-year-old woman was admitted to the “Prof. Dr. Ion Chiricuță” Oncology Institute, Cluj-Napoca, Romania, for a slowly progressively increasing goiter. Clinical examination confirmed the diagnosis of multinodular goiter, without lymph nodes metastases. Serum T3, T4 and TSH were in normal range. No fine needle aspiration biopsy (FNAB) was performed, neither ultrasonographic examination. Subtotal thyroidectomy was performed, without post-surgical complications. No frozen section analysis was request.

Macroscopic examination revealed the right thyroid lobe (4.2/2/0.5–1.8 cm) and the left lobe (4/1–3/0.8 cm) having a multinodular aspect. All nodules were less than 1 cm in size, with the exception of a nodule in the right lobe, having 1.2 cm in size, with whitish and solid aspect.

The specimen was fixed in 10% formalin solution, paraffin embedded, sectioned at 5 µm and histologically examined using standard Hematoxylin–Eosin (HE) staining method. Then, Congo red stain and the immunohistochemical (IHC) reaction with Ki-67 antigen (clone MIB-1, Novocastra, 1:80), using routine IHC procedures, were performed. Afterwards, the following IHC reactions were performed: calcitonin (Dako, 0.5:800), calretinin (Dako, 1:500), chromogranin A (Dako, 1:500), CK7 (Dako, 1:400), CK19 (Novocastra, 1:100), CEA (carcinoembryonic antigen, Dako, 1:50), E-cadherin (Dako, 1:50), galectin-3 (Novocastra, 1:200), HMB45 (Dako, 2:500), NSE (Dako, 1:500), synaptophysin (Dako, 1:500), S100 (Dako, 1:400) and thyroglobulin (clone DAK-Tg6, Dako, 1:500).

Two years after subtotal thyroidectomy, the patient is alive and free of disease.

**Results**

Histological examination revealed a nodular colloid macro-follicular hyperplasia in all nodules, having less than 1 cm in diameter. The larger nodule (1.2 cm) was located in right lobe and had an incomplete encapsulation, with a predominant trabecular-alveolar growth pattern of medium-to large-sized cell having acidophilic, clear
or vacuolated ill-defined cytoplasm. There was neither follicle formation, nor colloid (Figure 1). Tumor cells had nuclear abnormalities: irregular shape and borders, sometimes grooves, or intranuclear cytoplasmic pseudo-inclusions (Figure 2). Mitotic figures were rather rare. The cells were separated by fragments of acellular hyaline material (Figure 3), resembling amyloid, but having a negative amyloid (Congo red) stain. The most unusual fact was the strong cytoplasmic and membrane immunoreactivity for Ki-67 (Figure 4). In the nodule, the mitotic index could not be calculated, because the nuclei were covered by the membranous and cytoplasmic Ki-67 strong positivity reaction, compared with the surrounding thyroid (Figure 5). In this situation, we have been determined to appeal to some additional immunohistochemical techniques and we found the following results: thyroglobulin, CK7 and E-cadherin strongly positive; calcitonin, calretinin, chromogranin A, CK19, HMB45, synaptophysin and S100 protein were negative; CEA, galectin-3 and NSE – with weakly positive focal spot.

Figure 1 – Predominant trabecular architecture, with cells arranged in trabeculae separated by hyalinized stroma, infiltrated by some small lymphocytes (HE staining, 200×).

Figure 2 – Small clusters of tumor cells with enlarged nuclei, some of them having nuclear abnormalities: irregular shape and borders, perinucleolar vacuoles or intranuclear cytoplasmic inclusions (HE staining, 400×).

Figure 3 – Cells with clear or vacuolated ill-defined cytoplasm, separated by fragments of acellular hyaline material (HE staining, 400×).

Figure 4 – Strong cytoplasmic and membrane reactivity, giving an outline more obvious to the trabecular growth pattern (Ki-67 immunostaining, 200×).

Figure 5 – To the left, the nuclei are unobservable, covered by cytoplasmic Ki-67 positivity reaction. On the right-hand side, separate by a thin fibrous interface, the surrounding thyroid has some mitotic figures – Ki-67 positive (Ki-67 immunostaining, 200×).

Discussion

The hyalinizing trabecular tumor is a rare lesion. Since 1987, when it was for the first time described by Carney et al. [1], in the specialty literature about 100 cases have been communicated.

The HTT is considered a controversial lesion because some authors have classified it as a separate benign entity [1], and others as a variant of sclerosant thyroid carcinoma [2, 3]. Moreover, some authors have argued that HTT may be associated with other thyroid diseases: as multinodular goiter, chronic lymphocytic thyroiditis, or follicular adenomas [4, 5].

The case, which we present in this paper, is an unexpected morphological discovery in a multinodular goiter.

HTT occurs more often in women than in men, between the fourth and seventh decade of age, as presented our
case. It is unusual to be met less than 30 years and over 80 years.

As reported in the literature, the diagnosis of HTT can be rarely established pre-operatively by FNAB alone, or intra-operatively by frozen tissue section [7–9].

All the authors agree that the diagnosis of HTT cannot be established only using usual stains, because it can be misdiagnosed as a papillary carcinoma, or a medullar carcinoma, or a parangangioma [2, 4, 5, 7, 8, 10–14]. That is why is absolutely necessary to perform some immunohistochemical studies.

In our case, the lesion’s aspects observed using only HE staining suggested the following five possible diagnoses: an atypical hyalinizing trabecular adenoma, an encapsulated variant of papillary carcinoma with hyalinizing trabecular pattern, a medullar carcinoma, a primary parangangioma of the thyroid, and a metastatic thyroid melanoma.

Because the tumors included in the differential diagnosis had rather a similar morphology, immunohistochemistry was essential in distinguishing the correct diagnosis. These five differential diagnoses led to apply Congo red stain and the following IHC reactions: calcitonin, calretinin, chromogranin A, cytokeratins 7 and 19, CEA, galectin-3, HMB-45, Ki-67 antigen, neuron-specific enolase (NSE), synaptophysin, S100 protein, and thyroglobulin.

The negative CK19 and S100 immunoreactivity removed papillary carcinoma (which has a strongly and diffusely positive reaction). The absence of amyloid (Congo red negativity), and the negative calcitonin and positive thyroglobulin immunoreactivity have eliminated medullar carcinoma. Unlike primary parangangioma of the thyroid (where cells are positively stained to chromogranin A, synaptophysin, NSE, and S100 protein), in our case, although NSE had a weak focal positive reaction, chromogranin A and synaptophysin immunoreactivity were negative. So, primary parangangioma of the thyroid has been excluded. In the same way was excluded a metastatic thyroid melanoma by HMB-45 and S100 negative reactions. Thus, only hyalinizing trabecular adenoma diagnosis remained in question. With small focal intensity differences, the immunoreactions of our case coincided with the data from literature.

To determine the proliferative index of the lesion, we used the immunostaining with Ki-67 antibody. Surprisingly was the fact that the mitotic index could not be revealed, the cell nuclei being covered by a very thickened, with collagen fibers penetrating in the basal membrane. The nuclei showed nucleoli and nuclear pores. There are rare cases in which cells had a clear cytoplasm, irregular limits, forming unequal chords separated by tiny capillaries. Nuclei had slight anisokaryohromia. Unequal follicles without colloid were separated by dense connective tissue bands”. Making ultrastructural examinations, Prof. Taşcă explained that the “folicular cells were linked by a tight junction and rare collagen fibers existed towards the basal membrane. The nuclei showed nucleoli and nuclear pores. There are phagolysosomal aggregate in cells cytoplasm”. He tried to highlight the ultrastructural difference between the intensity of fibrosis in the rare cases of adenomas with clear cell cytoplasm and hyalinizing PC. Therefore, in chapter with “folliculopapillary adenocarcinoma”, Prof. Taşcă described “neoplastic cells having basal membrane thickened, with collagen fibers penetrating in the basal membrane near the plasmalemma” [21].

**Conclusions**

There is no doubt that immunohistochemistry is essential in distinguishing HTT from other thyroid lesions, but the most of immunohistochemical stains may be carried out only as support of a differential diagnosis. In HTT, the examination of Ki-67 immunohistochemical stain is of essential importance. Without it, the diagnosis is very difficult to establish.

**Acknowledgments**

This paper is set to be a homage paid to the Romanian...
Professor of pathology Constantin Taşcă (1929–1994), whose death took place 20 years ago. He had substantially contributed to the development of knowledge of endocrine pathology in Romania.

**Author contribution**
Authors have equal contribution to this paper.

**References**


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