Hürthle (Oncocytic) Cell Tumors of Thyroid: Etiopathogenesis, Diagnosis and Clinical Significance

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The etiopathogenesis and the classification of oncocytic (Hürthle cell) tumors of the thyroid is reviewed with an emphasis on the role played by mitochondrial and nuclear genetic abnormalities that interfere with mitochondrial function. Oxyphilia is classified into primary or secondary and the so-called Hürthle cell carcinoma is divided into oncocytic (Hürthle cell) variants of papillary and follicular carcinoma. *Int J Surg Pathol 13(1):29–35, 2005

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It is difficult to find a subject in thyroid oncology that has been more mistreated than that of Hürthle (oncocytic) cell tumors. The problems started a couple of decades ago when it was said (and widely accepted) that all oncocytic tumors of the thyroid were malignant. This claim was disproved by several groups in the 1970s/1980s, but the confusion persisted with regard to the clinicopathologic singularity of the carcinomas with oncocytic features, which were thought to represent a group of thyroid neoplasms that should be placed into a category independent from those of papillary and follicular carcinoma (for a review, see references 1–3).

We know now that the oncocytic lesions of the thyroid (and of other organs) may be nonneoplastic or neoplastic and, within the latter, benign or malignant. We also know that these lesions are composed of cells stuffed with mitochondria with morphologic, functional, and genetic abnormalities. It is estimated that a full-blown oncocytic cell has 4,000 to 5,000 mitochondria, whereas an eosinophil or a sperm cell has about 30 mitochondria; the human cell with more abundant mitochondria is the oocyte which has about 1,500 mitochondria (for a review, see references 3–5).

Etiopathogenesis

The accumulation of mitochondria in the cytoplasm of the oncocytic cells may be due to a primary alteration of the mitochondrial DNA (mtDNA) that...
encode mitochondrial enzymes [6]. Regardless of the mechanism involved in the process, any deficient mitochondrial function leads to an increased number of mitochondria through the stimulation of mitochondrial proliferation (via transcription factor(s) encoded by the nucleus) [3,6]. It is not known yet whether a decreased turnover of the mitochondria may also contribute to their accumulation in oncocytic cells.

The most typical mtDNA alteration in oncocytic cells is the presence of a large deletion (about 5 kb that corresponds to one third of the total DNA in each mitochondrial chromosome) [7]. This large deletion is usually designated by “common deletion” and has been detected in oncocytic cells of Hashimoto’s thyroiditis and all sorts of oncocytic tumors of the thyroid, as well as in Warthin’s tumor of the salivary glands [7–9]. Point mutations in the mitochondrial genes encoding for enzymes of the complexes I, III, IV, and V of the mitochondrial respiratory chain (MRC) have also been reported in oncocytic tumors of the thyroid [6].

The mitochondria containing deleted and/or mutated mtDNA proliferate more than “normal” mitochondria, thus leading to a progressive increase in the percentage of abnormal mitochondria in the cells’ cytoplasm [3].

Mutations in the nuclear genes encoding for enzymes of the MRC or the Krebs cycle may also lead to an increased number of mitochondria, provided the deficient mitochondrial function triggers a compensatory proliferation of the organelles [3].

The main difference between the mtDNA and the nDNA pathway concerns the hereditary aspects. If one is dealing with nDNA germline mutations, the condition is inherited as a mendelian trait, whereas the same does not hold true when mtDNA is involved (the mtDNA dependent disorders are maternally inherited and do not follow the mendelian rules) [10].

The pathogenic mechanism leading to a progressive accumulation of mitochondria provides a basis to support the claim that the oncocytic transformation is not a black and white phenomenon—the mitochondria accumulate for years in the cytoplasm of cells that are not dividing or are slowly dividing. The process starts by cells with a normal number of mitochondria and progresses toward cells with slightly increased mitochondria (oncocytic cells, Fig. 1) until reaching a full-blown status of oncocytic cells. The time lapse needed to allow the accumulation of mitochondria may be relatively long and explains why oncocytic cells are prominent only in old or relatively old patients with Hashimoto’s thyroiditis (patients with Hashimoto’s thyroiditis younger than 20 rarely present oncocytic cells) [3].

This pathogenic mechanism also explains the existence of oncocytic (oxyphilic, eosinophilic) cells in tumors of parenchymatous organs (thyroid, parathyroids, kidneys, salivary glands, adrenals) and/or in endocrine/neuroendocrine tumors, regardless of the organ of origin, whereas they are extremely rare in carcinomas of GI tract, respiratory tract, skin, and so on. The mitochondria can accu-

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**Fig. 1.** Thyroid adenoma composed of cells with a relatively large and granular cytoplasm—oncocytic cells.
mulate only in cells of tumors that are not actively dividing, i.e., relatively slow growing neoplasms; in rapidly growing neoplasms the division of the cytoplasm of the neoplastic cells prevents the accumulation of the mitochondria. Following this line of reasoning it makes sense that most oncocytic tumors are benign or low malignant neoplasms (example: renal oncocytomas). The only exception appears to be some oncocytic carcinomas of the thyroid (see below).

The mechanism of tumor formation under these circumstances is not yet well understood. Several possibilities have been advanced: (1) The mitochondrial abnormalities block (in one way or another) the apoptotic process, increasing the survival of the cells [11]. (2) The deficient mitochondrial function is sensed as a hypoxic stimulus leading to increased levels of the inducible form of the hypoxic inducible factor (HIF-1), which triggers some proangiogenesis pathways (and also proliferation?) (for a review on these two possibilities see reference 10).

In Fig. 2 we have summarized the most important steps of oncocytic (Hürthle cell) tumorigenesis.

The study of sporadic and familial forms of papillary thyroid carcinoma (PTC) with oncocytic features has shown that it is likely that the occurrence of such tumors depends both on the mitochondrial alterations—which would lead to hyperplastic lesions and/or benign tumors—and 1 or several oncogenic steps (in the case of PTC these steps may be rearrangements of rearranged during transfection [RET]/PTC or TRK, or a V-Raf murine sarcoma viral oncogene homologue B1 [BRAF] mutation). It is this concept that is represented in Fig. 3.

The timing of the occurrence of the oncogenic step(s) leads to 2 different situations: The so-called primary and secondary oxyphilia, in which either all the tumor cells, or only a part of them, present oncocytic features, respectively (Figs. 4, 5).

**Diagnosis**

It is now almost unanimously accepted that the oncocytic appearance of thyroid follicular cells is a phenotypic trait that may occur in all sorts of benign and malignant lesions: Hashimoto’s thyroiditis, nodular goiters, adenomas, and carcinomas. The same holds true for thyroid c-cells and cells of other organs and/or tumors (medullary carcinoma of the thyroid, parathyroids of old individuals, several types of endocrine and neuroendocrine tumors).

In the group of thyroid carcinomas there is enough clinicopathologic evidence to support the concept that every type of carcinoma has its oncocytic counterpart. This concept has been incorporated in the forthcoming edition of the WHO Classification in which the “old” Hürthle (oncocytic) carcinoma is substituted by oncocytic variants of papillary carcinoma, follicular carcinoma, and poorly differentiated carcinoma [12]. It is extremely rare to see oncocytic features in an undifferentiated

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**Fig. 2.** Schematic representation of the most important steps in oncocytic (Hürthle cell) tumorigenesis.
MtDNA alterations
nDNA $\rightarrow$ mt alterations

Cell growth (benign tumour) + “Oncogenic Step(s)

CANCER

Fig. 3. Schematic representation of oncocytic (Hürthle cell) carcinogenesis.

carcinoma, probably because the neoplastic cells of this type of tumor divide too rapidly to allow the accumulation of mitochondria.

Despite acknowledging the existence of some controversies, most authors claim that the typical molecular features of conventional papillary and follicular carcinomas are also present in their oncocytic counterparts [12,13]. This has recently been shown by us with regard to the BRAF V600E. This mutation is detected in about 50% of conventional PTC as well as in about 50% of cases of the oncocytic variant of PTC [14,15]. It is also very prevalent in Warthin-like PTC, which is characteristically composed of oncocytic cells [15]. Curiously, the V600E BRAF mutation is not detected in the follicular variant of PTC (FVPTC), nor in cases of the oncocytic variant of PTC displaying a follicular growth pattern [15], thus supporting the concept that the oncocytic features do not interfere with the carcinogenic pathway.

The criteria used in the diagnosis of the oncocytic variants of PTC and follicular carcinoma are those
Fig. 5. A. Only part of the neoplastic cells in this conventional PTC display oncocytic features. B. Schematic representation of the histogenesis of so-called secondary oxyphilia.

Fig. 6. Oncocytic variant of PTC. Notice the oncocytic features and the PTC-like nuclei.

used in the diagnosis of conventional tumors: Mainly the nuclear characteristics in PTC (Fig. 6) and the signs of capsular and/or vascular invasion in follicular carcinoma. The same holds true regarding the diagnosis of variants of PTC such as the papillary microcarcinoma [16], as well as the diagnosis of the recently described “well-differentiated tumor of uncertain malignant potential” and “well-differentiated carcinoma, not otherwise specified” [12,17]. In every setting the presence of oncocytic cells should not interfere with the diagnostic criteria.

Clinical Significance

The prognosis of patients with oncocytic variant of PTC is similar to that of patients with conven-
Fig. 7. Oncocytic variant of follicular carcinoma. Macroscopic (A) and low-power histologic appearance (B) showing foci of hemorrhagic necrosis.

...tional PTC (and the same holds true regarding follicular carcinomas) provided the age of the patients and the staging of the tumors are comparable [12,18]. The only negative aspect of oncocytic carcinomas of the thyroid is their lesser ability to trap iodine, thus rendering them less responsive to radioactive iodine [3].

Three last clinicopathologic points on these tumors: (1) Although it is now widely accepted that many oncocytic tumors are benign (oncocytic adenomas), one still keeps the concept that the percentage of oncocytic tumors displaying signs of invasiveness is higher than in their conventional counterparts (take-home lesson: One should go on searching actively for capsular and vascular invasion, and for PTC nuclei, in oncocytic tumors that look benign at a first glance) [1,2,12]. (2) Benign and malignant oncocytic tumors tend to suffer ischemic necrosis, mainly after fine needle aspiration (Fig. 7). The reasons behind this finding, which may be linked to the apoptosis blockage exhibited by oncocytic tumor cells, are discussed by Máximo and Sobrinho-Simões [3]. (3) There are well-documented familial thyroid tumors exhibiting prominent oncocytic features. These tumors may be benign (usually multiple adenomas) or malignant (PTC or follicular carcinoma, occasionally arising in preexisting benign, oncocytic lesions). Several nuclear genes encoding for enzymes of MRC or Krebs cycle are apparently involved in these familial cases [10,19].

References

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