Immunohistochemical Diagnosis of Thyroid Tumors

Guido Fadda, MD, MIAC*, Esther Diana Rossi, MD, MIAC, PhD

KEYWORDS

• Thyroid carcinoma • Immunochemistry • Prognosis • Target therapy

ABSTRACT

Recent insight into the molecular mechanisms of thyroid carcinogenesis has led to studies involving newly directed antibodies. With the introduction of new molecular targeted therapies, these antibodies may represent useful predictors of therapeutic response in tumors unresponsive to radioiodine or insensitive to conventional antitumor therapies. These markers complement the development of markers that are able to discern benign from malignant entities, including hyalinizing trabecular tumors, oncocytic neoplasms, and follicular variant of papillary thyroid carcinoma. The use of antibodies directed to proteins generated by mutated genes may represent a cost-effective method for diagnosing and managing patients affected by thyroid tumors.

OVERVIEW

Thyroid neoplasms represent the most common endocrine tumors, with an incidence of 8.7 cases/100,000 people per year in Europe, although overall mortality is less than 0.1% in all tumor cases[1,2]

The classification of thyroid neoplasms[3] includes benign and malignant epithelial tumors derived from either follicular cells or parafollicular common (C) cells. Papillary thyroid carcinoma (PTC) is the most thyroid cancer, accounting for almost 90% of all thyroid malignancies, often with a favorable course characterized by frequent nodal spreading but uncommon distant metastases. PTC includes 2 main tumor subtypes: classical type and follicular variant. The former exhibits the distinctive papillary structures from which the name derives whereas the histologic hallmark of the latter is the predominantly microfollicular pattern, lacking true papillae. Regardless of the architecture, the diagnosis of PTC relies on distinctive nuclear features (clearing, elongation, grooves, and pseudoinclusions), which are usually shared by all histotypes, the latter rarer in the follicular variant.

Some cases of PTC show obvious infiltration of surrounding tissues in addition to either invasion of an associated tumor capsule or the adjacent vessels, manifesting the malignant nature of the tumor. On the other hand, some cases, of follicular variant, for instance, are encapsulated and lack invasion, and the histologic definition of carcinoma can be questionable.

Thyroid epithelial malignancies include follicular thyroid carcinoma (FTC), approximately 5% of thyroid carcinomas, characterized by a proliferation of follicular cells (thyrocytes) showing variably pleomorphic and variably chromatic nuclei. The distinction between FTC and its benign counterpart, follicular adenoma (FA), relies on the detection of histologic parameters of invasion, capsular and/or vascular invasion. If only one of such features is observed in a follicular-patterned, nonpapillary neoplasm, a diagnosis of FTC is warranted. These parameters for malignancy apply similarly to tumors composed exclusively of Hürthle (or oxyphilic or oncocytic) cells, FTC, and oncocytic (Hürthle cell) type (Hurthle cell carcinoma [HCC]), with oncocytic changes thought to result from hypoxic changes of the thyrocytes. FTC and HCC are more likely to metastasize to distant sites, such as lung and bone, rather than the local lymph node and neck involvement seen in PTC.

The authors do not have conflicts of interest to disclose.
Division of Anatomic Pathology and Histology, Agostino Gemelli School of Medicine and Hospital, Catholic University, Largo Francesco Vito, Rome 1 00168, Italy
* Corresponding author.
E-mail address: guidofadda@rm.unicatt.it

Surgical Pathology 7 (2014) 491–500
http://dx.doi.org/10.1016/j.path.2014.08.002
1875-9181/14/$ – see front matter

Other thyrocyte-derived malignancies include poorly differentiated thyroid carcinoma (PDTC) and undifferentiated (anaplastic) thyroid carcinoma (ATC). They represent no more than 3% of all thyroid carcinomas and the majority of thyroid-related mortalities. Of the nonfollicular thyroid malignancies, the most important are medullary thyroid carcinoma (MTC) and non-Hodgkin lymphoma.

IMMUNOHISTOCHEMISTRY

Immunohistochemistry (IHC) was introduced in the early 1970s into routine pathology practice. It has been traditionally used in thyroid pathology for the identification of the cell origin in differentiated tumors arising in the gland or metastasizing outside it, such as thyroglobulin, calcitonin, or parathyroid hormone.[4] There are some tumor types which immunophenotyping deserves a more detailed discussion. Hyalinizing trabecular tumors (HTTs) are uncommon neoplasms with morphology that overlaps that of PTC. HTT exhibits a trabecular pattern with hyalinization of the stroma composed of thyrocytes showing intranuclear pseudoinclusions resembling those of PTC and, in some cases, RET/PTC rearrangements.[5,6] This tumor, however, is generally of low malignant potential.[7] Leonardo and colleagues[8] have proposed an immunohistochemical method for differentiating HTT from PTC. Namely, cytoplasmic (membranous) expression of MIB-1 antibody, directed toward the cell-cycle protein Ki-67, instead of nuclear expression of Ki-67, which is used as proliferative index in many tumors. The unusual experimental conditions (room temperature instead of 37°C) and the strict histologic criteria for diagnosing pure forms have somewhat hindered the diffusion of this diagnostic marker.

Hürthle cell tumors (HCTs) (or oxyphilic and oncocytic tumors) are included in the category of follicular thyroid tumors, although they do not share all of its histologic characteristics. Hürthle cells, thought to be a metaplastic change of thyrocytes due to either local hypoxia or hormone withdrawal, show a distinctive morphology, with large pleomorphic nuclei and abundant granular cytoplasm which, at the ultrastructural level, is rich in mitochondria and responsible for the oncocytic features of HC seen by hematoxylin-eosin stain and, by IHC, for the mild nonspecific positivity of these cells in a majority of IHC reactions. Thus, the real positivity of Hürthle cells should be assessed only in presence of a strong expression in the majority of the cellular component (like thyroglobulin usually does) or when the antibody expression is primarily nuclear (like thyroid transcription factor-1 [TTF-1]). The IHC stains that are helpful in the other differentiated tumors (such as galectin-3, Hector Battifora mesothelial antigen [HBME-1], and cytokeratin [CK] 19; discussed later) provide controversial results in HCT and are regarded as unreliable for discriminating benign from malignant neoplasms. Some studies involving HCT have reported that some proliferative markers, such as Ki-67 and cyclin D1, may be of help in this differential diagnosis.[9] A different approach to oncocytic tumors has been studied by Gasparre and colleagues.[10] They have observed that the oncocytic metaplasia, originated by a marked increase of the mitochondrial component in the cytoplasm of the follicular cells, is often associated with a nonsense mutation of the ND-5 subunit of the respiratory chain complex I of the mitochondria. The expression of the human mitochondrial antibody (HMA) against this subunit reveals the presence of oncocytic cells, regardless of their malignant nature. In this case, the HMA does not represent a marker of malignancy but, nonetheless, this is an important parameter to take into account for a diagnosis of follicular-patterned neoplasm because oncocytic cells sometimes are misdiagnosed as PTC cells. The diagnosis of PTC does not require capsular or vascular invasion, unlike oncocytic carcinomas, which are diagnosed on the basis of invasion. Thus, the expression of HMA in a wholly encapsulated follicular neoplasm favors the diagnosis of benign oncocytic adenoma whereas its negativity suggests a papillary carcinoma.

Medullary thyroid carcinoma can be easily distinguished from follicular neoplasms by calcitonin expression. Cytoplasmic calcitonin expression, however, may be weak or the antibody may leak in the normal parenchyma, hindering the correct interpretation of the morphologic picture, especially when the tumor is of small size or in presence of a C-cell hyperplasia. Usually, C cells show a concomitant bright, albeit nonspecific, positivity for carcinoembryonic antigen, chromogranin A, bombesin, synaptophysin, and other neuroendocrine markers.[4] Recently, aquaporins (AQPs) 3 and 4 have been investigated in MTC in comparison with differentiated follicular-derived tumors showing a distinct pattern of expression: AQP-4 exhibits the same positivity as thyroglobulin whereas AQP-3 results distinctively negative in PTC and FA and positive in the cytoplasm membrane of C cells.[11]

ATCs lose the distinctive immunophenotype of follicular-derived thyroid carcinomas, such as the expression of thyroglobulin and TTF-1. Diagnosis of ATC relies mainly on tumor morphology with