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Review

Histopathology of Thyroid Tumors. An Overview

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INTRODUCTION

Thyroid cancer accounts for approximately 1% of total cancer cases in developed countries. It affects all age groups, although it is rare in children. Thyroid tumors are more frequent in women than in men. Despite their relative rarity they exhibit a wide range of morphological patterns and biological behavior which may explain the great interest in these neoplasms of both pathologists and clinicians.

Another issue of considerable interest is the molecular abnormalities involved in thyroid tumor pathology. In this review, following the histologic classification of thyroid neoplasms with their histologic and cytologic variants, a brief discussion of some of the most relevant molecular alterations recently described will be undertaken.

A. HISTOPATHOLOGY

The thyroid gland contains two major types of epithelial cells: the follicular cells, which convert iodine into thyroxine and triiodothyronine, and the parafollicular or C-cells, which secrete calcitonin. Thyroid tumors can originate from these very different kinds of cells or from nonepithelial stromal elements, and architectural, cytologic and histogenetic features have been taken into consideration for neoplasms classification. According to the World Health Organization (WHO)[1] primary thyroid tumors are classified as epithelial and nonepithelial, benign or malignant, with a separate category for lymphomas and miscellaneous neoplasms (Table 1). A slightly different classification scheme has been adopted by the Armed Forces Institute of Pathology (AFIP)[2], giving priority to the cell of origin and incorporating, in each cell type, special tumor types and subtypes designated as "variants" (Table 2). This review is based on the AFIP classification.

The traditional classification of thyroid cancer as well differentiated carcinomas (papillary and follicular) characterized by relatively good prognosis, or poorly differentiated carcinomas (follicular, anaplastic) associated with aggressive behavior, metastases and death, is no longer applicable since certain morphologic variants of papillary carcinoma are associated with poor prognosis. In addition, the existence of true mixed forms of papillary and follicular cancers has been disproved, while new entities such as "mixed follicular-parafollicular carcinoma" have emerged[3].

The criteria for the recognition of follicular and papillary carcinomas have changed in recent years but both denominations have been retained. Papillae no longer seem to be necessary for the diagnosis of papillary carcinoma, and cytologic features such as oncocytic, clear cell, squamous and mucinous changes have resulted in the designation of special tumor types and subtypes. The practical importance of these special types resides in differential diagnosis rather than their biological behavior[2].

Key words: Thyroid, Thyroid histopathology, Tumors, Oncogenes

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Table 1. Histologic Classification of Thyroid Tumors (WHO)[1]

I. Epithelial Tumors
A. Benign
1. Follicular adenoma
2. Others
B. Malignant
1. Follicular carcinoma
2. Papillary carcinoma
3. Medullary carcinoma
4. Undifferentiated (anaplastic) carcinoma
5. Others
II. Nonepithelial Tumors
A. Benign
B. Malignant
III. Malignant lymphomas
IV. Miscellaneous
V. Secondary tumors
VI. Unclassified tumors
VII. Tumor-like lesions

A.1. TUMORS OF FOLLICULAR CELLS AND THEIR VARIANTS

A.1.1. Follicular Adenoma

Follicular adenoma is defined as a benign encapsulated tumor with follicular cell differentiation showing a uniform pattern throughout the confine nodule (Figure 1A). The fibrous capsule varies in thickness, but is usually thin. Follicular adenomas are solitary tumors with a solid, homogeneous cut surface, but hemorrhage and cystic degeneration are not uncommon. Their size is highly variable, ranging from 1 cm to over 10 cm. On the basis of microscopic features, several variants have been described, including oncocytic adenoma (Hürthle cell adenoma), adenoma with clear cell change, atypical adenoma, hyalinizing trabecular adenoma, adenoma with bizarre nuclei and rare types such as adenoma with adipose (adenolipoma) or cartilagenous (adenochondroma) metaplasia[2]. Recent studies suggest that hyalinizing trabecular adenoma, also described as hyalinizing trabecular tumor

Table 2. Classification of Thyroid Tumors (AFIP)[2]

PRIMARY TUMORS
1. Epithelial tumors
A. Tumors of follicular cells
Benign: Follicular adenoma (conventional, variants*)
Malignant: carcinoma
differentiated
follicular carcinoma
papillary carcinoma (conventional, variants**)
poorly differentiated (insular carcinoma, others)
undifferentiated or anaplastic
B. Tumors of C-cells (and related neuroendocrine cells)
medullary carcinoma
others
C. Tumors of follicular and C-cells
mixed medullary-follicular carcinoma
2. Sarcomas
3. Malignant lymphoma (and related hematopoietic neoplasms)
4. Miscellaneous neoplasms
SECONDARY TUMORS
TUMOR-LIKE LESIONS

* oncocytic, clear cell changes, atypical adenoma, hyalinizing trabecular, with bizarre nuclei

** microcarcinoma, encapsulated, follicular, tall/columnar cell, diffuse sclerosing, solid/trabecular

and "paraganglioma-like adenoma of the thyroid", may be related to papillary carcinoma at the molecular level[4,5], while others propose a multidirectional differentiation from pluripotent primitive cells[6]. Some of these controversial issues are challenged by Lloyd[7] who concludes that additional studies are needed to clearly define this entity. Until then, it would seem appropriate to regard and treat hyalinizing trabecular adenoma as a benign neoplasm[2]. "Toxic" adenoma is a clinical rather than a pathologic entity, defining only those hyperfunctioning lesions in which clinical manifestations occur, and not any "hot" adenoma[2].

A.1.2. Follicular Carcinoma

Most authors agree that only follicular tumors that exhibit vascular and/or capsular invasion should be regarded as follicular carcinomas[8]. Depending on the degree of their invasiveness, follicular carcinomas have been divided into two major categories: minimally invasive or encapsulated (the most common), and widely invasive. The frequency of follicular carcinoma among thyroid malignancies ranges from 5-10% in non-iodine-deficient areas to 30-40% in iodine-deficient areas[2].

Macroscopically, follicular carcinomas do not differ appreciably from follicular adenomas. The fibrous capsule surrounding the tumor tends to be thicker and more irregular than in adenomas[2]. Minimally invasive follicular carcinoma is an encapsulated tumor showing capsular and/or vascular invasion only on microscopic evaluation, while the widely invasive neoplasm shows lack of complete encapsulation, extensive areas of invasion to the adjacent thyroid tissue and/or widespread blood vessels infiltration[2,8].

Immunohistochemistry, morphometry, ploidy analysis, cytogenetic and oncogene markers have failed to provide reliable information concerning the distinction between follicular carcinoma and follicular adenoma. The current diagnostic criteria for malignancy are still the histologic assessment of true capsular infiltration (the tumor must penetrate the entire thickness of the capsule) and/or invasion of blood vessels in or beyond the capsule (Figure 1B)[2,8-10]. It is apparent that minimally invasive follicular tumors cannot be accurately diagnosed by fine needle aspiration (FNA) cytology since the crucial diagnostic criteria are missing[2,9,11]. Similar problems exist in evaluating such lesions by frozen section[2,11,12].

Malignant thyroid tumors composed exclusively or predominately (over 75%) of oncocytes (Hürthle cell tumors) share some similarities with follicular carcinomas as regards the clinical presentation, the architectural features and the degree of invasiveness, and therefore should be considered as a variant of follicular carcinoma[2,8,9]. However, some authors have suggested that the morphologic features and natural history of these tumors are distinctive enough that they be considered as a separate entity[13,14].

A.1.3. Papillary Carcinoma

Papillary carcinoma is the most common type of thyroid cancer, comprising approximately 80% of all primary thyroid malignancies[15]. Classical or non-otherwise specified (NOS) papillary carcinoma is characterized by the formation of papillae and a set of distinctive nuclear features (optically clear appearance, overlapping, pseudoinclusions and nuclear grooves) (Figure 1C, 1D)[2,16-18]. The size of papillary carcinoma is extremely variable with a mean diameter of 2-3 cm[2]. A clinically detected tumor is usually confined to the thyroid, is presented as a fairly well circumscribed or infiltrative neoplasm and has an indolent course. Its mode of spread is most commonly via lymphatics within the thyroid leading to "multifocal" disease and to cervical node metastases[2,9]. Indeed, 50% or more of papillary carcinomas have nodal metastases at initial diagnosis[19].

There are several histologic variants of papillary carcinoma, some of which are associated with a more guarded prognosis (Table 3)[10].

A.1.3.a. Variants of papillary carcinoma

a.1. Papillary microcarcinoma: The term refers to papillary carcinomas measuring 1cm or less in diameter and replaces the older designation of occult sclerosing carcinoma, also known as nonencapsulated sclerosing tumor and occult papillary carcinoma[2]. Re-

Table 3. Variants of Papillary Carcinoma and their Prognosis[10]

Good	Variable	Guarded
Microcarcinoma	Oxyphilic cell	Diffuse sclerosing
Encapsulated	Follicular	Tall/columnar cell
Macrofollicular	Solid sclerosing	Diffuse follicular
	Solid/trabecular	
	With nodular fasciitis-like stroma	

cently, at the 12th Annual Cancer Meeting held at Porto, Portugal, a consensus was reached by a group of experts to rename this entity as papillary microtumor[20]. Papillary microcarcinomas are frequently detected as incidental findings in autopsy or in surgical specimens and are associated with an excellent prognosis despite occasional regional lymph node metastases. The reported incidence in autopsy material has ranged from 4% to 35.6%[2,21-23].

a.2. Encapsulated variant: The tumor is totally surrounded by a fibrous capsule which may be intact or focally infiltrated by the tumor. These tumors have an exceptionally good prognosis and, although some lesions have shown lymph node involvement, distant metastases or death due to tumor are practically nonexistent[24].

a.3. Follicular variant: Papillary carcinomas having an exclusive or almost exclusive follicular pattern are designated as a follicular variant of papillary carcinoma. The biologic behavior of this variant is analogous to that of conventional papillary carcinoma. The metastases may have a mixed papillary and follicular formation. A diffuse or widely invasive form of the follicular variant and macrofollicular variant of papillary carcinoma have also been described[25,26].

a.4. Tall and columnar cell variant: The main histologic feature of the tall cell variant of papillary carcinoma is the presence of "tall" cells (the height being twice the width), with an intense eosinophilic cytoplasm, lining well-developed papillae (Figure 1E). In the columnar cell variant, there is a marked nuclear stratification and the cytoplasm is clear, sometimes with subnuclear vacuolization[2,9]. Both the tall cell and columnar cell variant are said to be more aggressive than classical papillary carcinomas[27,28]. However, recent studies suggest that the clinical behavior of these rare types of papillary carcinoma depends on tumor size, extrathyroidal invasion and distant metastases[29,30].

a.5. Diffuse sclerosing variant: This is an unusual form of papillary carcinoma first described by Vickery et al[22], who noticed that it more frequently affects children and is associated with a poor prognosis. This tumor is characterized by diffuse involvement of one or two lobes and clinically may be misdiagnosed as Hashimoto's thyroiditis[2]. Its hallmark, microscopically, is the presence of widespread intrathyroid lymphatic permeation by numerous neoplastic micropapillae.

a.6. Other variants: Variants such as solid variant, clear cell and oxyphilic variant, papillary carcinoma with lipomatous stroma, Warthin's-like tumor or with nodular fasciitis-like stroma and cribriform papillary carcinoma have been reported, but they are too few in number for an adequate assessment of their prognostic implication[2,15,31]. The term solid and/or trabecular variant is used when a NOS papillary carcinoma has a solid and/or trabecular pattern throughout the tumor[2].

A.1.4. Poorly Differentiated Carcinoma

Poorly differentiated thyroid carcinoma represents a heterogeneous group of malignant neoplasms, with various histologic patterns of growth and different biologic behavior, that lie somewhere between well-differentiated and undifferentiated carcinomas[6,31-33]. The heterogeneity of these tumors reflects the different terms used to describe and diagnose this entity, including solid, trabecular, insular, poorly differentiated, intermediate type, less well-differentiated and follicular carcinoma with insular component[2,32-35].

Macroscopically, poorly differentiated carcinomas usually present as large (>5 cm in diameter), solid, unencapsulated, nodular or multinodular, grey-white tumors that tend to invade perithyroidal tissues[2,15,33]. Microscopically, the majority of these tumors show a trabecular, solid or insular growth pattern[10]. A combination of other histologic features such as follicles, columnar cell carcinoma, papillary, follicular and Hürthle cell carcinoma foci have been found[2,31-33].

Recent studies on molecular and genetic features of poorly differentiated carcinomas provide evidence that there is a link between these tumors and the papillary thyroid carcinoma, and they support the concept that poorly differentiated carcinoma represents an immediate step in the progression from well-differentiated to undifferentiated carcinomas[36,37]. However, a divergent histogenesis must also be considered since poorly differentiated carcinomas exhibit, in addition to the usual thyroglobulin immunoreactivity, focal immunoreactivity to neuroendocrine markers, such as calcitonin, neurotensin and somatostatin[33,35,38].

Apart from tumor stage, clinicopathologic features such as tumor necrosis, mitotic count (>3/10HPF) and the age (>45 years) of the patient, have been reported as being significantly associated with the clinically aggressive behavior of these tumors[32,33].

A.1.5. Undifferentiated (Anaplastic) Carcinoma

Undifferentiated thyroid carcinomas account for 5-10% of all primary malignant tumors of the thyroid[2]. These tumors, usually present in elderly patients (mean age 60-65 years), are rapidly growing, with massive local invasion and early distant metastases, most frequently to lung, adrenals and bone[2,9].

Undifferentiated thyroid carcinoma exhibits a wide spectrum of morphologic types, singly or in combination. The three major patterns of growth are squamoid (morphologic similarity to nonkeratinizing squamous cell carcinoma), spindle cell (sarcoma-like growth) and giant cell (numerous osteoclast-like multinucleated giant cells, resembling giant cell tumor of the bone or soft tissues) (Figure 1F). Features common to all three types are high mitotic activity, extensive necrosis and a marked degree of invasiveness within the gland as well as to the extrathyroidal structures[2,9].

Areas of pre-existing well-differentiated thyroid tumor (more often follicular or papillary carcinoma) can be seen in many, if not most, undifferentiated carcinomas. On the other hand, the undifferentiated tumor may develop months or years after the removal of a well-differentiated thyroid neoplasm. These findings support the hypothesis that undifferentiated thyroid tumors arise from pre-existing well-differentiated thyroid carcinomas[2,39].

A.2. TUMORS OF C-CELLS AND THEIR VARIANTS

A.2.1. Medullary Carcinoma

Medullary thyroid carcinoma is a malignant tumor of the thyroid which shows evidence of C-cell differentiation and usually contains calcitonin (Figure 1G)[2]. It accounts for up to 10% of all malignant thyroid tumors[2,15]. The variants of medullary carcinoma are: glandular (composed in part of tubular or follicular structures and may resemble follicular carcinoma), papillary (exhibiting true papillary pattern of growth), small cell (resembling the intermediate variant of small cell carcinoma of the lung), and giant cell (occasionally present or focal areas with giant cell formation). Less common are the clear cell, melanotic (pigmanted), oncocytic (oxyphilic), squamous, amphicrine (calcitonin and mucin-producing cells) and paraganglioma-like variants[2,40].

A.2.2. Mixed follicular–parafollicular Carcinoma

Mixed medullary and follicular carcinoma are rare neoplasms which show morphologic features of both follicular and C-cell differentiation[41]. The dual differentiation has also been noted in their metastatic sites. These neoplasms must be distinguished from the follicular variant of medullary carcinoma and from medullary carcinoma with entrapped normal follicles. Thus, WHO is very strict in defining them as "tumors showing both the morphologic features of medullary carcinoma together with immunoreactivity for calcitonin and the morphologic features of follicular carcinoma together with immunoreactivity for thyroglobulin"[42].

Whether these tumors represent collision tumors or arise from a stem cell capable of dual differentiation into follicular and C-cell elements is the subject of several excellent reports in the recent literature[3,43,44].

A.3. CYTOPLASMIC CHANGES IN THYROID TUMORS

A.3.1. Tumors with oncocytic features: Oncocytes (oxiphilic cells, "Hürthle cells") are derived from follicular epithelium, characterized morphologically by large size, distinct cell borders and abundant granular acidophilic cytoplasm, large nucleus and prominent nucleolus. The cytoplasmic granularity is produced by an increased number of huge mitochondria. Oncocytic thyroid tumors (oncocytic adenoma/carcinoma) are composed exclusively or predominately of follicular cells exhibiting oncocytic features[2]. However, isolated cells or groups of follicular cells with oncocytic features can be seen in other conditions such as radiated thyroids, aging thyroids, nodular goiter, "nonspecific" chronic thyroiditis or Hashimoto's thyroiditis and Graves' disease. In addition, several neoplasms of the thyroid (oncocytic papillary neoplasms, Warthin-like tumor of the thyroid, tall cell variant of papillary carcinoma) exhibit oncocytic features[9,45].

A.3.2. Tumors with clear cell features: Clear cell changes can occur in any of the major histologic types of benign and malignant thyroid neoplasms. They have also been observed in nodular hyperplasia and in Hashimoto's thyroiditis[2]. The clearing of the cytoplasm may be the consequence of intracytoplasmic accumulation of vesicles (of mitochondrial or other origin: Hürthle cell tumors, follicular tumors), glycogen (papillary

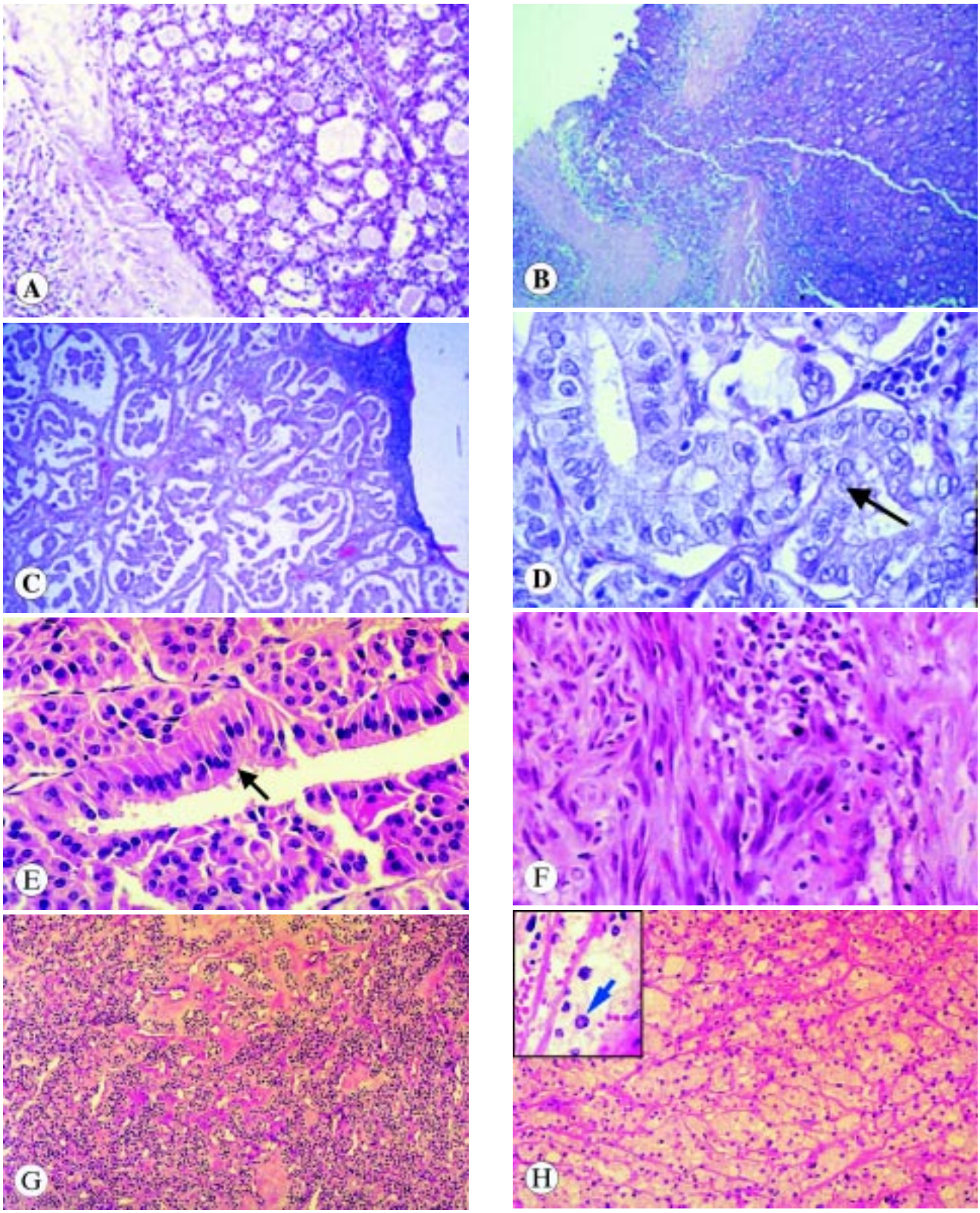

Figure 1. Histology of Thyroid Tumors. **A.** Follicular adenoma: note the sharp separation of a follicular tumor from the surrounding tissue by a uniform fibrous capsule. **B.** Follicular carcinoma with capsular penetration. **C.** Papillary carcinoma metastatic to a lymph node: typical appearance of papillary carcinoma with complex and branching papillae. **D.** Higher magnification showing optical clear, overlapping and grooved (arrow) nuclei. **E.** Tall cell variant papillary carcinoma, lined by tall cells (arrow). **F.** Undifferentiated carcinoma with elongated tumor cells. **G.** Medullary carcinoma. **H.** Papillary carcinoma with clear cell changes: typical intranuclear inclusion (inset).

carcinoma) (Figure 1H), lipid (undifferentiated carcinoma), thyroglobulin and "mucin"[2].

A.3.3. Tumors with squamous features: Squamous cells in the thyroid can originate from a remnant of the thyroglossal duct or ultimobranchial body or may be the result of squamous metaplasia in Hashimoto's thyroiditis, papillary carcinoma or other conditions[9]. Focal or extensive squamous differentiation has been described in papillary carcinoma, undifferentiated carcinoma, follicular neoplasms and medullary carcinoma[2].

A.3.4. Tumors with mucinous features: Mucosubstances have been detected in several thyroid tumors, either in the cytoplasm of the tumor cells or extracellulary[46,47]. Primary thyroid tumors that have been found to contain mucin include signet ring follicular adenoma, mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma with eosinophilia, papillary, undifferentiated and medullary carcinoma[2].

A.4. THYROID SARCOMAS

Sarcomas arising in the thyroid are extremely rare. Various microscopic types have been reported in the form of isolated case reports, including fibrosarcoma[48], liposarcoma[49], leiomyosarcoma[50], chondrosarcoma[51], osteosarcoma[52,53] and malignant schwannoma[54].

It is likely that most thyroid neoplasms resembling sarcomas are examples of undifferentiated (sarcomatoid) carcinomas. In addition, cartilage and bone production in association with benign and malignant thyroid lesions have been observed[39,55]. However, the distinction between true thyroid sarcomas and sarcoma-like undifferentiated carcinomas is of little importance since the natural history and response to therapy of both entities do not differ significantly. They occur in elderly patients, are rapidly growing and are uniformly fatal[9]. The sarcoma that apparently does arise in the thyroid is angiosarcoma. It occurs predominately in Alpine regions of central Europe where it typically arises in a gland with multinodular goiter[56]. Although several investigators have suggested that this entity actually represents a vascular variant of undifferentiated carcinoma, some of these tumors exhibit anastomosing vascular channels, Wiebel-Palade bodies ultrastructurally, immunoreactivity for factor-VIII related antigen and other factors consistent with endothelial differentiation[57].

A.5. MALIGNANT LYMPHOMAS

Primary non-Hodgkin lymphomas of the thyroid are now considered to be tumors of mucosa-associated lymphoid tissue (MALT)[15]. They constitute about 8% of all thyroid malignancies[2]. Primary thyroid lymphomas have a B cell phenotype and are highly associated with lymphocytic or Hashimoto's thyroiditis[2,15]. Thyroid malignant lymphomas are most common in adult or elderly women, clinically presented in the form of an enlarged thyroid, leading to symptoms of tracheal or laryngeal compression when extended outside the gland[2,9]. Most patients are euthyroid[58]. Since MALT lymphomas characteristically metastasize to sites that contain similar tissue, it is not uncommon to see a lymphoma of the thyroid with concomitant involvement of the gastrointestinal tract[30,59].

Other primary lymphoid tumors include plasmacytoma and Hodgkin lymphoma[2].

A.6. SECONDARY TUMORS OF THE THYROID

Although any malignant tumor can metastasize to the thyroid gland, the latter is an infrequent site of tumor metastases. Direct extension into the thyroid may occur in carcinomas of the pharynx, larynx, trachea and esophagus[2,9]. Most of these neoplasms are of squamous cell type. Retrograde lymphatic spread into the thyroid, although unusual, has been reported, with breast carcinoma being the most frequent[9]. Hematogenous metastases to the thyroid, particularly of malignant melanoma, lung, gastrointestinal, breast and renal cell carcinomas are commonly encountered at autopsy series[2,9]. Rare sources of primary tumors, such as choriocarcinoma, malignant phylloides tumor and osteosarcoma, have also been reported[60]. Some metastases are found in preexisting thyroid lesions, such as breast carcinoma into papillary carcinoma and lung and renal cell carcinoma into follicular adenoma[2,61-63]. Particularly diagnostically challenging are metastases of unknown origin. Of these the most common are renal cell carcinoma, large bowel adenocarcinoma and malignant melanoma[9].

Metastatic disease to the thyroid may present a diagnostic problem for the following reasons: a) Many cases are asymptomatic and too small in size to be detected clinically; b) The primary site is difficult to identify histologically, in small biopsy samples (FNA), since many metastatic lesions are poorly or moder-

ately differentiated (and sometimes undifferentiated) carcinomas; c) Metastases could be manifested long after the detection of a primary tumor (as long as 26 years); d) Many clinically detected lesions are solitary rather than multiple[60,64].

B. MOLECULAR MARKERS OF THYROID TUMORS

Several types of oncogene alterations have been described as possible mechanism(s) for thyroid tumorogenesis. Whether these alterations can serve as markers, predicting the biological behavior of thyroid tumors or confirming unclear diagnoses is a matter of debate. For a comprehensive review on molecular abnormalities involved in thyroid tumorogenesis see Sagev et al[65].

B.1. RAS Oncogene

RAS oncogenes (K-ras, H-ras, N-ras) activation has been identified in tumors originating from the follicular epithelium of the thyroid gland. Point mutations in ras oncogenes are more common in follicular adenoma and carcinoma than in papillary carcinoma as well as in tumors from iodide-deficient areas[66,67]. Some studies suggest that ras activation is an early event in thyroid carcinogenesis while others indicate an association between ras mutations and tumor progression[68,69].

B.2. RET Oncogene

The RET (rearranged during transfection) oncogene encodes two isoforms of a transmembrane tyrosine-kinase receptor, which is involved in the development of the neural crest and kidney[70]. A common genetic alteration in thyroid tumors is the rearrangements of the RET oncogene leading to the so-called RET/PTC (for papillary thyroid carcinoma) oncogene[71]. Experimental studies have indicated that the RET/PTC oncogene is specifically involved in the pathogenesis of thyroid tumors with morhpologic features of papillary carcinomas, while a high prevalence of RET/PTC rearrangements have been reported in radiation-induced papillary carcinoma, especially in children affected in the Chernobyl reactor accident[70-73]. It is of interest that spontaneous RET mutations are also associated with familial and sporadic medullary carcinomas[65].

Recent studies showed that RET/PTC was more frequently expressed in papillary microcarcinomas than in clinically manifest tumors, and poorly differentiated thyroid cancer has a low prevalence in RET activation[36,74]. It therefore appears that rearrangement of RET/PTC is an early event in papillary thyroid carcinoma development and is less important in tumor progression.

B.3. p53

The p53 tumor suppressor gene is the most frequent mutated gene in human cancer. With regard to the thyroid, p53 gene mutations are rarely observed in differentiated tumors and are more commonly found in poorly differentiated and anaplastic carcinomas[75,76]. The high p53 protein expression in undifferentiated carcinomas, compared to papillary carcinomas, and the absence of mutations in the residual papillary component suggest that p53 genetic alterations are late events in the sequence of thyroid carcinogenesis and could be linked to their reported worse prognosis[77,78].

B.4. MET

c-MET oncogene encodes a tyrosine kinase acting as the receptor for hepatocyte growth factor/scatter factor (HGF/SF), a powerful mitogen for epithelial cells, including thyroid follicular cells[65,79]. MET overexpression is associated with the papillary thyroid carcinoma phenotype, particularly its aggressive forms, being negative in medullary carcinomas and low or absent in poorly differentiated tumors[79,80]. Data on the significance of MET overexpression in thyroid tumors are inconsistent. Some studies found MET overeactivity to be associated with advanced tumor stage and histologic variants with poor prognosis, while others showed a relationship between negative/low expression and vascular invasion and distant metastases[79,81].

C. CONCLUSIONS

Thyroid tumors can originate from follicular epithelium, from parafollicular or C cells or from nonepithelial stromal components. The traditional classification of thyroid cancer as well differentiated carcinomas, characterized by relatively good prognosis, or poorly differentiated carcinomas associated with aggressive behavior, metastases and death, is no longer applicable since certain morphologic variants of papillary carcinoma are associated with poor prognosis.

The hyalinizing trabecular adenoma of the thyroid remains a controversial entity, while the concept of poorly differentiated carcinoma still constitutes a complicated issue. The practical importance of the various cytoplasmic changes seen in thyroid lesions resides on differential diagnosis rather than their biological behavior. Several types of molecular alterations occurring in thyroid tumors are under investigation in order to enhance our understanding of the possible mechanisms of thyroid tumorogenesis. The clinical significance of these studies remains to be defined.

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