Thyroid Tumors With a Follicular Growth Pattern

Problems in Differential Diagnosis

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- Tumors of the thyroid characterized by a follicular growth pattern constitute the most common type of lesion of this organ encountered by pathologists. The vast majority of such lesions do not pose difficulties for histopathologic interpretation. A subset of these tumors, however, can represent a serious challenge for diagnosis. Thyroid tumors with a follicular growth pattern include a broad range of lesions that range from benign, hyperplastic nodules to follicular adenomas to follicular carcinomas. In addition, other types of tumors belonging in separate diagnostic categories can also present histologically with a follicular growth pattern, including the follicular variant of papillary thyroid carcinoma and medullary carcinoma. The histologic features and diagnostic criteria used for distinguishing among these conditions can often be subtle and subjective.

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The problems involved in the histopathologic interpretation of thyroid tumors with a follicular growth pattern have been repeatedly alluded to in the literature.1-5 The main problems seem to involve the distinctions between hyperplastic nodules and follicular adenoma,1,5 between follicular adenoma and minimally invasive follicular carcinoma,2,5,6 and between follicular adenoma/carcinoma and the follicular variant of papillary carcinoma.2,3,5,7 Immunohistochemistry and molecular pathology for genetic profiling have been utilized in an attempt to resolve some of these issues but have not yet succeeded in attaining a level of reliability or practicality that could be translated into the routine practice of surgical pathology.8-10

HYPERPLASTIC NODULE VERSUS FOLLICULAR ADENOMA

The distinction between hyperplastic nodules and follicular adenoma has been a controversial topic for many years due to the current inability to confidently demonstrate the neoplastic versus hyperplastic nature of a given thyroid nodule by conventional means. Follicular adenoma is currently defined as an encapsulated, benign neoplastic proliferation of thyroid follicles. The problem is that hyperplastic nodules can also be completely or partially encapsulated and may very closely resemble their neoplastic counterparts. Features that have been traditionally invoked to make this distinction include the presence in hyperplastic nodules of a cell population within the tumor identical to that of the uninvolved surrounding thyroid parenchyma, as opposed to a different cell population in adenomas, and the presence of multiple nodules in hyperplasia versus a solitary lesion in adenoma. Exceptions to these rules and overlapping features exist, however, making them unreliable parameters. Another finding that has been thought to be helpful for the morphologic distinction between these two conditions is the presence of degenerative changes within the nodule, a feature that is thought to favor a hyperplastic process over an adenoma. However, adenomas with stromal hyalinization, metaplastic bone formation, cystic changes, hemorrhage, and degeneration of collagen can also be encountered. Diagnostic criteria thus vary among experts and across institutions.

DeMay1 at the University of Chicago favors a diagnosis of nodular goiter over adenoma when a lesion occurs against a background of any significant damage to the thyroid (ie, “nodularity”) and if the interior of the lesion is variable or shows evidence of degeneration. Baloch and LiVolsi2 at the University of Pennsylvania restrict the diagnosis of adenoma to lesions that show a distinct growth pattern (which may be microfollicular, macrofollicular, or trabecular), are confined within the boundaries of a capsule, and show a different growth pattern from the surrounding thyroid parenchyma.

I consider any follicular lesion that is not well encapsulated and shows evidence of hyperplastic changes elsewhere in the gland as a manifestation of nodular hyperplasia regardless of its cell composition or growth pattern, presence or absence of regressive changes, and similarity or dissimilarity to the surrounding thyroid parenchyma. I restrict the diagnosis of follicular adenoma to lesions that are well encapsulated and usually solitary, and in which the uninvolved thyroid parenchyma does not display any features of nodular hyperplasia. For practical purposes, the distinction may be more of academic interest than of practical value, since both are, by definition, benign conditions. Recent evidence seems to indicate that the two lesions may be more closely related than previously thought and that adenomas may simply represent a more advanced step within a hyperplasia-adenoma sequence of
thyroid cellular progression. Several investigators have shown that up to 70% of hyperplastic nodules are clonal proliferations, and that monoclonal and polyclonal nodules may coexist within these lesions.

**FOLLICULAR ADENOMA VERSUS MINIMALLY INVASIVE FOLLICULAR CARCINOMA**

Follicular carcinoma of the thyroid represents the malignant counterpart of follicular adenoma. Because follicular carcinomas are, for the most part, devoid of the conventional cytological attributes of malignancy (ie, nuclear enlargement, hyperchromatism, mitotic activity, tumor cell necrosis), their diagnosis is in large part predicated on the demonstration of capsular or vascular invasion. Of these two, the criteria of capsular invasion are the more difficult to apply and remain highly controversial. A consensus regarding what constitutes capsular invasion is still lacking, even among experts, and varies widely among practicing pathologists. Moreover, some studies have indicated that capsular invasion in the absence of vascular invasion does not appear to significantly affect the outcome of these tumors. Issues such as whether focal infiltration into the capsule as opposed to complete penetration through the entire capsule represents evidence of malignancy continue to be debated. Some pathologists are willing to defensively interpret even minimal irregularities in the capsule as evidence of capsular invasion in follicular neoplasms. The problem is compounded for tumors that are incompletely encapsulated, in which areas devoid of a capsule or in which the capsule is very attenuated can be easily interpreted as foci of thyroid parenchymal invasion.

Because invasion represents the only valid morphologic parameter for the diagnosis of these tumors, follicular carcinoma of the thyroid generally has been divided into “minimally invasive” and “widely invasive.” The histologic appearance of the tumor cells in both lesions can be identical, the only difference residing in the extent of the invasion. To qualify as widely invasive, a tumor must show extensive capsular and vascular invasion and penetrate beyond the confines of the thyroid proper. Tumors with more limited invasive qualities are generally categorized as minimally invasive. Baloch and LiVolsi have further subdivided minimally invasive tumors into those showing only capsular invasion and those showing vascular invasion with or without capsular invasion, the latter of which they term grossly encapsulated angioinvasive follicular carcinoma. Recently, the group of pathologists who reviewed the thyroid tumors from children and young adults involved in the Chernobyl nuclear accident have proposed that tumors with minimal invasion of the capsule be designated as “well-differentiated tumor of indeterminate malignant potential” or “follicular tumor of uncertain malignant potential,” since the majority of those cases behaved in an indolent manner. Some reluctance has been expressed about the use of this terminology, mainly based on reports of rare cases in which tumors with minimal capsular invasion showed distant metastases. Although there must be no question that exceptions to all rules can occur in nature, and that a very small number of cases can occasionally behave in an unexpected manner and display paradoxically aggressive behavior, the bulk of the evidence suggests that the majority of follicular tumors that metastasize are those associated with either extensive transcapsular invasion and/or un-
Minimal irregularities of the capsule should not be considered as evidence of capsular invasion in follicular neoplasms of the thyroid (hematoxylin-eosin, original magnification ×100).

Focal attenuation and disappearance of the capsule in follicular neoplasm of the thyroid that can be confused with evidence of capsular invasion (hematoxylin-eosin, original magnification ×100).

Through-and-through invasion through the capsule in minimally invasive follicular carcinoma (hematoxylin-eosin, original magnification ×20).

The follicular variant of papillary thyroid carcinoma (FVPTC), a distinctive subtype of papillary carcinoma first recognized by Lidsay, is currently defined as a thyroid malignancy with a predominant or exclusive follicular growth pattern displaying the characteristic nuclear features of papillary thyroid carcinoma. The tumors can be infiltrative or encapsulated. Recognition of the FVPTC poses many problems at different levels. The diagnosis of this tumor by fine-needle aspiration cytology and during intraoperative frozen section examination is notoriously difficult and unreliable. Studies have reported a very low sensitivity with fine-needle aspiration for the identification of FVPTC, and this experience has been largely paralleled on intraoperative frozen section examination. The majority of these tumors can only be reliably identified upon review of permanent sections from surgically resected lesions. Difficulties for diagnosis can also arise during the evaluation of permanent sections when the distinctive nuclear features of papillary thyroid carcinoma are either not well developed or only present focally within the lesion. Multiple studies have demonstrated great interobserver variability in the diagnosis of these tumors, even among experts in thyroid pathology, thus underscoring the difficulties in properly defining the criteria for the diagnosis of this particular type of papillary thyroid carcinoma. This fact has immediate practical consequences for these patients, as overdiagnosis of this condition may lead to excessive treatment, including total thyroidectomy followed by radioactive iodide therapy. This acquires a particular importance with the encapsulated variant of FVPTC, which is associated with an excellent prognosis and for which distant blood-borne metastasis has rarely been documented.

The most difficult circumstance for diagnosis arises when these tumors are well circumscribed and encapsulated. Such lesions may be the most difficult to recognize as FVPTC, and proper diagnosis can only be achieved when the overwhelming majority of the tumor cells display the characteristic features of papillary thyroid carcinoma. Unfortunately, pathologists’ perceptions of what constitute the characteristic features of papillary carcinoma can vary widely. Another significant problem is posed by encapsulated tumors in which the features of papillary thyroid carcinoma are only present focally or in multiple microscopic foci (Figures 4 and 5). Several approaches have been offered for such tumors, including rendering a diagnosis of multifocal papillary thyroid carcinoma arising in a benign nodule, making a diagnosis of follicular tumor of uncertain malignant potential, or considering the entire nodule as a FVPTC.

Numerous studies have investigated the role of immunohistochemical staining and molecular tumor assay for separating FVPTC from other, benign conditions.
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fortunately, the majority of such markers have been
deemed to be insufficiently discriminatory to make a re-
liable diagnosis on problematic encapsulated follicular les-
ions. The majority of the markers employed so far, in addi-
tion to not being consistently expressed in all cases of FVPTC, have also been demonstrated in other thyroid conditions, including hyperplastic nodules and follicular adenomas. The case has also been made for the notion that molecular profiling of slow-growing tumors such as the majority of adenomas and differentiated thyroid carcino-
mas may not accurately reflect their ultimate clinical fate. For example, even if a low-grade or morphologically benign lesion were found to have a RET rearrangement, this would have no bearing on the patient's prognosis if the tumor was adequately resected. Some authors have predicted that the more pathologists study oncogene expression in these tumors, the more molecular genetic classifications will become increasingly complex, and gradations matching those seen by morphology will eventually emerge. It can thus be very easy to argue that the gold standard for the diagnosis of these tumors remains their morphology as observed under routine microscopy with standard hematoxylin-eosin–stained sections.

Many different approaches have been advocated for the correct diagnosis of FVPTC. The current perception is that this type of tumor is frequently overdiagnosed by pathol-
ologists. In a recent study, the most important morpho-
clogic criteria used to identify FVPTC offered by a panel of expert thyroid pathologists included cytoplasmic invaginations with pseudonuclear inclusions, abundant nuclear grooves, and ground glass nuclei. This group of expert thyroid pathologists also experienced fewer difficulties in properly identifying FVPTC in tumors that were widely invasive and showed clear-cut capsular or vascular invasion than in encapsulated lesions. LiVolsi and Baloch favor making a diagnosis of FVPTC on any encapsulated lesion that shows any areas with the characteristic cyto-
logic features of papillary thyroid carcinoma. Chan has proposed much more stringent criteria for the diagnosis of such lesions, including the evaluation of major and mi-
nor features. The four major features cited by Chan for the diagnosis of encapsulated FVPTC are (1) oval rather than round nuclei; (2) crowding of nuclei, with lack of polarity in the follicles; (3) clear or pale nuclear chromatin pattern throughout the entire lesion, or prominent nuclear grooves; and (4) presence of psammoma bodies. If only 1 of these 4 features is absent, the presence of all of the following subsidiary features would need to be encoun-
tered to establish the diagnosis: (1) presence of abortive papillae, (2) predominantly elongated or irregularly shaped follicles, (3) dark-staining colloid, (4) presence of rare nuclear pseudoinclusions, and (5) multinucleated histiocytes in the lumen of the follicles. Like Chan, I also favor the idea of following a more stringent approach to the diagnosis of the encapsulated variant of FVPTC. Unfortunately, in the present litigious climate, many pathologists and even some experts prefer to apply very lax criteria for making this diagnosis for fear of being sued for missing a malignancy. The risk of missing an aggressive malignancy, however, appears to be overrated because, as pointed out previously by several authors, the majority of studies to date have shown that such tumors are not associated with any significant risk of recurrence or metastasis. In light of this, the proposal by the group of Chernobyl pathologists for designating lesions in which incomplete or equivocal features are present as “well-differentiated thyroid tumor of uncertain mal-
nignant potential” appears warranted and preferable to an outright diagnosis of carcinoma, which often leads to un-
necessary aggressive treatment.

References


