

Cytologic Analysis of Follicular Lesions of the Thyroid Gland

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Fine Needle Aspiration (FNA) of the thyroid is a valuable tool in the evaluation of thyroid nodules. Papillary carcinoma can be diagnosed with remarkable accuracy. Medullary carcinoma, anaplastic carcinoma, metastatic carcinomas, and malignant lymphoma can be identified, also. Benign entities (such as adenomatoid nodules and Hashimoto's thyroiditis) can be recognized as well. Lesions with follicular patterns are diagnostic problems on FNA smears (1) and in histologic sections as well (2).

What is a follicular lesion of the thyroid gland?

It is a mass or nodule composed almost exclusively of thyroid follicles. The latter are glandular structures that usually contain colloid. Based on their size, when compared to normal thyroid follicles, they are identified as micro- or macro-follicles. This description applies to histologic sections, but their appearance is different in cytologic specimens. Macrofollicles and normal-sized follicles usually appear as sheets and clusters of follicular cells in the smears. Microfollicles appear as glandular structures with well-defined lumens that are either empty or contain inspissated colloid. Also, the follicular cells from hyperplastic nodules (adenomatoid nodules) often are arranged as rosettes and tubules (1).

What are the types of follicular lesions?

Follicular lesions may be benign or malignant (1-3).

Benign:

Adenomatoid nodule (hyperplastic nodule): Usually its histologic pattern is heterogeneous with small and large follicles and evidence of degenerative changes, it is not encapsulated, and the background is that of multinodular goiter. FNA smears contain follicular cells arranged in sheets, clusters, rosettes, and tubules. Some foamy histiocytes and occasional multinucleated giant cells are seen. The amount of colloid is variable.

Follicular adenoma: Usually it is a single lesion, has a relatively homogeneous histologic pattern (microfollicular, macrofollicular and/or trabecular), is devoid of degenerative changes, and is encapsulated. The histology of the gland is otherwise normal. On FNA smears we cannot determine whether a follicular tumor is benign (adenoma) or malignant (carcinoma). Hence, we make a "generic" diagnosis of follicular neoplasm. The smears contain a variable number of follicular cells, usually dependent on the skill of the aspirator. These tumors bleed easily and hemodilution of the sample is common. The neoplastic follicular cells are frequently larger than the normal follicular epithelial cells. They are arranged in rosettes, tubules, and microfollicles (with empty lumina or containing inspissated colloid). The background is hemorrhagic and almost devoid of colloid.

Malignant:*Follicular carcinoma.*

Low grade follicular carcinoma (grossly well defined, encapsulated, minimally invasive)

Not low grade follicular carcinoma (grossly well defined, extension through the entire thickness of the capsule, infiltration of adjacent parenchyma without an intervening layer of fibrous tissue, vascular invasion of any kind but particularly of large vessels, and focal necrosis)

High grade follicular carcinoma (often poorly differentiated, widely invasive).

Follicular variant of papillary carcinoma.

This is a common subtype of papillary carcinoma. Histologic sections reveal a variety of follicular structures, some markedly elongated, and minute or poorly formed papillary structures. The neoplastic cells have the distinctive appearance associated with the classic type of papillary carcinoma (large irregularly shaped nuclei, thick nuclear membranes, nuclear grooves, and relatively clear nuclei that have been referred to as “Orphan Annie eye” nuclei. Some dense connective tissue is seen frequently. FNA smears appear markedly cellular (4). Tissue fragments with microfollicles (most of them with empty lumens) are a frequent finding. The colloid is distinctive and frequently appears as “pink balls” on Diff-Quik stained smears. Nuclear grooves and “Orphan Annie eye” nuclei are not evident with the Diff-Quik stain.

Follicular variant of medullary carcinoma.

These are rare tumors in which a glandular pattern is conspicuous. Amyloid may be present.

Because of overlapping cytologic patterns, it is difficult or impossible to differentiate follicular adenomas from follicular carcinomas and from some cellular adenomatoid nodules. To separate a follicular adenoma from a follicular carcinoma we need histologic sections from the periphery of the lesion. The interface of the neoplasm with the thyroidal parenchyma has to be evaluated, as well as evidence of angioinvasion. This cannot be done on smears. Needless to say, the presence of distant metastases is also indicative of malignancy and therefore is the one clinical determinant of cancer. To complicate matters, there is no general agreement (due to lack of specific criteria) among pathologists regarding the diagnosis of hyperplastic (or cellular) nodules and follicular neoplasms. Likewise, there is confusion about capsular invasion (malignant lesion) and capsular entrapment (benign lesion). Capsular entrapment is not so common; it involves the inner aspect of the tumor’s capsule, and is not accompanied by vascular invasion. Hence, capsular invasion is more common; it may involve the entire thickness of the capsule, and is frequently accompanied by vascular invasion. We must note how the neoplastic cells relate to the adjacent fibrous tissue; they are arranged at right angles to the fibrous bundles. Needless to say, the number of histologic sections examined plays an important role in determining the true nature of the tumor.

Is conventional light microscopy enough for the differential diagnosis of follicular lesions?

The answer is a qualified NO. Light microscopy has shortcomings, but so far little progress has been made in the search for a magic tumor marker, and other ancillary studies have not solved the problem. In 2001, Thompson et al (5) stated that “No ultrastructural, morphometric, flow cytometry, immunohistochemical, or oncogene expression studies have proved to be reliably predictable in separating benign neoplasms from malignant neoplasms or between grades of malignant neoplasms. Therefore, a reliance on histomorphologic criteria alone, for the present, is the only way to separate between these categories.”

Role of immunohistochemical stains:

We have to emphasize that most of the studies deal with tissue samples and not with smears. CK19 can be helpful in the diagnosis of follicular variant of papillary carcinoma (6-8) but some follicular adenomas and follicular carcinomas (including the Hürthle cell variant) also stain positively (6). *ret*/PTC gene rearrangements have been reported as specific for the classic type of papillary thyroid carcinoma (8) and considerably less frequently in the follicular variant of papillary carcinoma (9). Other markers used to distinguish between benign and malignant follicular lesions are galectin-3 (10,11) and HBME-1 (8,12); these have proven to lack specificity.

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