correspondence

The Bethesda System for Reporting Thyroid Fine-Needle Aspiration Specimens

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To the Editor

The Bethesda System for reporting thyroid fine-needle aspiration (FNA) specimens[1] undoubtedly represents a major step toward standardization, reproducibility, and ultimately improved clinical significance, usefulness, and predictive value of thyroid FNA.

During the past decade, several classification schemes for thyroid gland FNA have been proposed by various professional organizations.[1-6] Most of these schemes consist of 4 to 6 diagnostic categories, which are not always comparable with each other. This variation has led to confusion and differences in perceptions of diagnostic terminology in cytopathology reporting of thyroid FNA between cytopathologists and clinicians.[7,8] The main difficulty is represented by "borderline" lesions characterized by atypia of undetermined significance and/or a microfollicular pattern.[9,10]

In this context, it is interesting to compare the division in 6 classes proposed by the National Cancer Institute (NCI)[1,2] with the division in 5 classes proposed by the British Association–Royal College of Physicians in 2002[4,5] and modified by the Italian Society of Pathology and Cytopathology–Italian Section of the International Academy of Pathology in 2007.[6] All classification systems provide a category for nondiagnostic FNA samples, a category for benign lesions, and a category for malignant lesions. However, there are also notable differences. The NCI system, as illustrated in ▮Table 1▮, introduces 2 categories for borderline lesions: "atypia/follicular lesion of undetermined significance" and "follicular neoplasm or suspicious for a follicular neoplasm." Conversely, the British and the Italian reporting systems provide a single category for all borderline lesions, named follicular lesion and follicular proliferation, respectively. In addition, the British and the Italian systems provide numeric coding for each category.

The differences in reporting borderline lesions testify to the well-recognized difficulties in evaluating thyroid lesions belonging to a gray zone. However, the comparison of the aforementioned reporting systems raises concerns about wide acceptance of the Bethesda System and some important questions: (1) Are there strict morphologic quantitative and qualitative criteria recognizable in cytologic preparations that allow the division of borderline follicular lesions into 2 categories? (2) If so, are these criteria adequate to ensure satisfactory interobserver and intraobserver diagnostic reproducibility? (3) Are they uniformly applicable? (4) Could they vary significantly depending on the operator

▮Table 1▮
Thyroid Classification Schemes

National Cancer Institute	British Association–Royal College of Physicians		Italian Society of Pathology and Cytopathology–Italian Section of the International Academy of Pathology	
Nondiagnostic	Thy1	Nondiagnostic	Tir1	Nondiagnostic
Benign	Thy2	Nonneoplastic/negative	Tir2	Negative for malignant cells
Atypia/follicular lesion of undetermined significance	Thy3	All follicular lesions	Tir3	Indeterminate (follicular proliferation)
Follicular neoplasm or suspicious for follicular neoplasm				
Suspicious for malignancy	Thy4	Suspicious for malignancy	Tir4	Suspicious for malignancy
Malignant	Thy5	Diagnostic of malignancy	Tir5	Malignancy

performing the FNA procedure? Are these criteria affected by quantitative and qualitative issues, such as representative cellularity and adequate fixation of the smears? (5) Can these criteria, by themselves, provide sufficient information on which to decide the management of patients with nodular thyroid lesions? (6) Are they prototypes of clear diagnostic terminology?

The attempt to answer these questions takes us back to the meaning and role of thyroid FNA. We know that FNA has proven to be accurate in the triage of patients with thyroid nodules.[11-13] However, to us, it remains a tool that must be integrated with other diagnostic procedures, such as ultrasonographic and scintigraphic examination of the thyroid gland. We believe that only a multidisciplinary approach can ensure the best results and that diagnostic accuracy with thyroid borderline lesions cannot rely solely on cytologic criteria. In addition, morphologic criteria are not only hindered by poor reproducibility[10] but also are affected by quantitative and qualitative variables that are strongly dependent on the expertise of the operator performing the FNA procedure. If we accept these intrinsic and extrinsic limits of thyroid FNA, the validity of splitting borderline lesions into 2 categories seems dubious. We should not forget that the recipients of cytopathology reports are patients and clinicians and that the latter are not always specialized in thyroid diseases. Do we really think that everyone understands the differences between follicular lesion of undetermined significance and "suspicious" for follicular neoplasm? Probably they do not. In this context, we should also acknowledge the fact that the word *suspect* might frighten more than the word *neoplasia* and might eventually lead to overtreatment. Finally, even if we manage to obtain good reproducibility among cytopathologists evaluating thyroid FNA and to correctly address terminology issues related to reporting, the clinical impact of the category follicular lesion of undetermined significance remains poor because, according to the Bethesda System, this category should be used as last resort and be limited to approximately 7% or fewer of all thyroid FNA samples.

We favor a 5-category classification system that links together all the borderline lesions and prefer the term *follicular proliferation* to *follicular neoplasm.* The cytopathologic evaluation of borderline lesions (Thy3 and Tir3) should always be accompanied by a microscopic description and, ideally, by brief management advice. It is critical to recognize that experience and technical procedures in performing thyroid FNA are just as important as evaluating the actual cytologic smears and that high technical quality of the specimens reduces the number of borderline lesions. In the final analysis, we believe that decisions about patients' management must be taken in a clinical context rather than on the basis of a given cytologic "diagnostic" category.

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The Authors' Reply

We appreciate the thoughtful letter from Drs Crippa and Mazzucchelli in response to our article summarizing the Bethesda System for Reporting Thyroid Cytopathology.[1] The authors raise a number of questions about thyroid cytopathology terminology, many of which were passionately debated during the Bethesda conference in 2007 and on the Web bulletin board that preceded the meeting in Bethesda. In particular, the relative merits of a 5- vs 6-class reporting system were reviewed. After considerable discussion, the majority of the participants elected a 6-class system that includes the category "atypia (or follicular lesion) of undetermined significance (AUS/FLUS)." Clearly, the validity of this 6-class system for reporting thyroid cytopathology results will need to be further examined as laboratories implement it in clinical practice. Preliminary data suggest, however, that including an AUS/FLUS category in the recommended terminology increases the sensitivity of the test.[2]

The need for AUS exists because there are definable cytomorphologic patterns that do not fit easily into other, well-accepted categories for reporting thyroid cytopathology results. What is one to do with the sparsely cellular specimen consisting mostly of microfollicles? Or the predominantly benign-appearing specimen that contains 1 or 2 groups with a few of the nuclear features of papillary carcinoma? Neither of these patterns fits comfortably into the benign category, but the changes are insufficient for any of the more serious categories that typically prompt lobectomy or thyroidectomy. For these patterns, a reasonable approach is a repeated FNA in 3 to 6 months; often the repeated FNA helps clarify the underlying biology.

As defined in this way, AUS/FLUS is a heterogeneous category. It is not simply the lower end of a pair of borderline categories whose upper end is the "follicular neoplasm/suspicious for follicular neoplasm" category. In many (but not all) cases, an AUS/FLUS interpretation is a consequence of a technically compromised specimen (eg, sparse cellularity or obscuring blood). In this regard, we agree with Crippa and Mazzucchelli when they say that "quantitative and qualitative variables…are strongly dependent on the expertise of the operator performing the FNA procedure."

The Bethesda atlas itself, which Crippa and Mazzucchelli did not have access to when they wrote their letter, defines and illustrates the morphologic criteria for the AUS/FLUS category.[3] An "atypical" category has been in use in many laboratories before, and we agree with Crippa and Mazzucchelli that its use has varied among pathologists and laboratories.[4] Indeed, it is the hope of all the participants in the Bethesda atlas project that the recently published atlas will provide a unified approach that will lead to greater consistency and better reproducibility.

The AUS/FLUS category may never have good interobserver reproducibility, even after pathologists familiarize themselves with the criteria in the atlas. But the lack of good reproducibility does not necessarily disqualify a diagnostic category. Pathologists frequently use diagnostic categories that have only fair-to-poor reproducibility; they do so because they believe certain distinctions are clinically important despite their less-than-ideal reproducibility.[5]

We agree with Crippa and Mazzucchelli that thyroid FNA is a "tool that must be integrated with other diagnostic procedures." Although each of the 6 categories of the Bethesda System for Reporting Thyroid Cytopathology has an implicit management recommendation, we acknowledge that clinical and sonographic findings, and even the patient's own desires, will often modify the management of a patient with a thyroid nodule. The FNA interpretation is, nevertheless, often the most important deciding factor. For this reason, the Bethesda terminology authors have taken care to emphasize that the recommended, usual management for an AUS/FLUS interpretation is a conservative one: a repeated FNA in 3 to 6 months.[6]

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