Chapter 2

Nondiagnostic/Unsatisfactory

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Background

In order to provide useful diagnostic information for optimal clinical management, a fine needle aspiration (FNA) sample of a thyroid nodule should be representative of the underlying lesion. A good criterion of adequacy, when appropriately applied, ensures a low false-negative rate. It is worth emphasizing, however, that cellularity/adequacy is dependent not only on the technique of the aspirator, but also on the inherent nature of the lesion (e.g., solid vs. cystic). In general, the adequacy of a thyroid FNA is defined by both the quantity and quality of the cellular and colloid components.

An assessment of specimen adequacy is an integral component of an FNA interpretation because it conveys the degree of certainty with which one can rely on the result. The definition of an adequate specimen in thyroid FNA is subjective and controversial. While the quality of a specimen is irrefutably critical to proper interpretation, controversy is introduced when rigid numerical criteria for cell quantity are imposed. No study supports any specific follicular cellularity as applicable to all cases (benign and malignant, cystic and solid) with high diagnostic accuracy. Additionally, there is no consensus supporting a minimum number of FNA passes required to obtain adequate samples. High quality specimens contain sufficient cells representative of a lesion to allow the observer to confidently render an accurate interpretation. High quality requires proficient collection combined with excellent slide preparation, processing, and staining.

Historically, the terms “nondiagnostic” and “inadequate/unsatisfactory” have been used interchangeably by some but not all cytopathologists: some cytopathologists (and endocrinologists) have interpreted the terms to mean different things.\(^1\) An unsatisfactory specimen is always nondiagnostic, but some technically satisfactory specimens may also be considered “nondiagnostic,” that is, showing nonspecific features not conclusively diagnostic of a particular entity. At the NCI conference, the terms “Nondiagnostic (ND)”
and “Unsatisfactory (UNS)” were recommended for the category that conveys an inadequate/insufficient sample. The Bethesda System is a flexible framework, however, and can be modified by the laboratory to suit the needs of its providers. Thus, if neither ND nor UNS appeals to providers, a more descriptive term like “Insufficient for Diagnosis” can be substituted. For the sake of simplicity, however, ND is used throughout the atlas to convey a sample that does not meet the adequacy criteria outlined below.

**Definition**

A specimen is considered “Nondiagnostic” or “Unsatisfactory” if it fails to meet the following adequacy criteria.

**Criteria for Adequacy**

A thyroid FNA sample is considered adequate for evaluation if it contains a minimum of six groups of well-visualized (i.e., well-stained, undistorted, and unobstructed) follicular cells, with at least ten cells per group, preferably on a single slide. Exceptions to this requirement apply to the following special circumstances:

1. *Solid nodules with cytologic atypia*. A sample that contains significant cytologic atypia is never considered ND/UNS. It is mandatory to report any significant atypia; a minimum number of follicular cells is not required.
2. *Solid nodules with inflammation*. Nodules in patients with lymphocytic (Hashimoto) thyroiditis, thyroid abscess, or granulomatous thyroiditis may contain only numerous inflammatory cells. Such cases are interpreted as Benign and not as ND/UNS. A minimum number of follicular cells is not required.
3. *Colloid nodules*. Specimens that consist of abundant thick colloid are considered Benign and satisfactory for evaluation. A minimum number of follicular cells is not required if easily-identifiable colloid predominates.

**Nondiagnostic/Unsatisfactory (Figs. 2.1-2.7)**

The following scenarios describe cases considered Nondiagnostic:

1. Fewer than six groups of well-preserved, well-stained follicular cell groups with ten cells each (see exceptions above)
2. Poorly prepared, poorly stained, or obscured follicular cells
3. Cyst fluid, with or without histiocytes, and fewer than six groups of ten benign follicular cells (see Explanatory Notes)
Figure 2.1. Nondiagnostic. The smear shows abundant red cells, with rare lymphocytes and monocytes. The sample is devoid of thyroid parenchymal elements. Some thyroid nodules are very vascular and on repeated passes yield only blood. Employing a smaller gauge needle (27 gauge), avoiding negative pressure, and employing a shorter needle dwell time within the nodule often results in better cellularity (smear, Diff-Quik stain).

Figure 2.2. Nondiagnostic. The smear shows a large fragment of skeletal muscle and no native thyroid tissue. This may occur when the needle traverses through the neck muscles. It is important not to confuse skeletal muscle with inspissated colloid (notice the cross striations in the muscle fragment, best seen at 7 o’clock) (smear, Papanicolaou stain).
**Figure 2.3.** Nondiagnostic. This FNA yielded ciliated respiratory epithelium from the trachea. Accidental puncture of the tracheal lumen is uncommon and typically happens in lesions of the thyroid isthmus. Such cases should be carefully evaluated for adequacy since they typically show only rare follicular epithelium (smear, Diff-Quik stain).

**Figure 2.4.** Nondiagnostic. Extensive air-drying artifact in this alcohol-fixed smear makes the cytologic interpretation difficult. Such cases should be carefully evaluated for adequacy and are best managed by a repeat FNA with rapid wet-fixation. Liquid-based cytology often resolves such issues and may be considered if air-drying artifact is a repeated problem (smear, Papanicolaou stain).
Figure 2.5. Nondiagnostic. Extensive obscuring blood hinders the evaluation of the follicular cells (smear, Papanicolaou stain).

Figure 2.6. Nondiagnostic (cyst fluid only). Abundant hemosiderin-laden macrophages and degenerated cyst fluid contents. Macrophages do not count towards specimen adequacy. Such cases, when devoid of significant background colloid, are interpreted as Nondiagnostic (smear, Papanicolaou stain).
Adequate samples are required to prevent false negative reports of thyroid lesions. Recommendations for adequacy generally apply only to the quantity of follicular cells and exclude consideration of macrophages, lymphocytes, and other nonmalignant cellular components. The ability to obtain follicular cells by FNA is dependent, in part, upon the nature of the lesion. The number of follicular cells necessary for a diagnosis is contingent upon the lesion aspirated because some lesions, such as benign cysts, do not yield many follicular cells.

Solid nodules with cytologic atypia should always be considered adequate and reported as abnormal (“Atypia of Undetermined Significance,” “Suspicious for Malignancy,” etc., depending on the findings), with a comment describing any limiting factor(s) such as scant cellularity. Follicular cells are not always present in aspirates of inflammatory lesions such as lymphocytic thyroiditis, thyroid abscesses, or granulomatous thyroiditis. Therefore, there is no minimum requirement for a follicular component when inflammation predominates. The presence of abundant colloid (as opposed to serum; Figs. 2.8 and 2.9) reliably identifies most benign processes.
**Figure 2.8.** Benign (satisfactory thyroid FNA). Abundant colloid coats the smear in this case of a "colloid nodule." Aspirates with large amounts of colloid are considered adequate for interpretation even when they contain less the six groups of follicular cells (smear, Diff-Quik stain).

**Figure 2.9.** Benign (satisfactory thyroid FNA). There is abundant dense colloid but only scant follicular cells (smear, Papanicolaou stain).
despite scant follicular cells.⁶ One group of follicular cells with features sufficient for the diagnosis of papillary thyroid carcinoma may constitute an adequate specimen in the proper clinical setting and should not be considered Nondiagnostic despite scant cellularity.⁷

Cyst fluid may yield only macrophages, but the risk of malignancy is low for these lesions if they are simple and under 3 cm.⁴,⁸,⁹ The cytopathologist is not always privy to clinical/sonographic information, however, and, in isolation, the possibility of a cystic papillary thyroid carcinoma cannot be excluded if a sample consists almost entirely of fluid and histiocytes. For this reason, such cases are reported as ND/UNS followed by the subcategory “Cyst fluid only” (See Sample Report 2). In the proper clinical setting (e.g., ultrasound evidence of a simple, unilocular cyst), these specimens may be considered clinically adequate, even though they are reported as ND/UNS.⁴

Occasionally, an adjacent anatomic site is aspirated, such as the trachea (Fig. 2.3) or sternocleidomastoid muscle (Fig. 2.2), yielding only nonthyroidal tissue. Such cases are considered ND/UNS.

There does not appear to be any difference in specimen adequacy using follicular cells in liquid-based preparations (LBP) as opposed to conventional smears. A minimum number of cell clusters is not as important as the total number of follicular cells in LBP, with 180–320 providing a diagnostic agreement of 80%.¹⁰

In the Bethesda System, unless a sample is interpreted as ND/UNS, it is considered satisfactory for evaluation.

**Management**

Nodules with an initial ND/UNS result should be re-aspirated, but no sooner than 3 months later; the 3-month interval is recommended to prevent false-positive interpretations due to reactive/reparative changes.¹¹ Ultrasound guidance with immediate, on-site adequacy evaluation is preferred for repeat aspiration after an initial ND/UNS specimen, especially for solid nodules. Repeating the FNA results in a diagnostic interpretation in up to 60% of cases.¹²,¹³ Most nodules with an ND/UNS interpretation prove to be benign.¹⁴,¹⁵ After two successive ND/UNS specimens, close clinical follow-up with ultrasound or surgery should be considered, depending upon the clinical findings. Since the risk of malignancy in cystic lesions is low, re-aspiration of most cystic nodules with an initial ND/UNS result should be performed only if the ultrasound findings are suspicious.
Sample Reports

Example 1 (solid nodule):
NONDIAGNOSTIC.
Specimen processed and examined, but nondiagnostic due to insufficient cellularity.
Note: A repeat aspiration should be considered if clinically indicated.

Example 2 (cystic lesion):
NONDIAGNOSTIC.
Cyst fluid only (see Note).
Specimen processed and examined, but nondiagnostic because the specimen consists almost exclusively of histiocytes; interpretation is limited by insufficient follicular cells and/or colloid.
Note: Recommend correlation with cyst size and complexity on ultrasound to assist with further management of the lesion.

Example 3:
UNSATISFACTORY.
Specimen processed and examined, but unsatisfactory due to poor fixation and preservation.
Note: A repeat aspiration should be considered if clinically indicated.

References


The Bethesda System for Reporting Thyroid Cytopathology
Definitions, Criteria and Explanatory Notes
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