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Efficacy of Ultrasound-Guided Fine-Needle Aspiration Biopsy in the Diagnosis of Complex Thyroid Nodules

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Cystic thyroid nodules are considered to be one of the major causes of nondiagnostic and false-negative results on conventional fine-needle aspiration biopsy, thus limiting the potential of this method for the evaluation of complex (solid-cystic) thyroid nodules. Although ultrasound-guided fine-needle aspiration biopsy has emerged as a highly effective diagnostic method for the assessment of nonpalpable and difficult to palpate nodules, its role in complex nodules has not yet been carefully evaluated. In this study, we report the efficacy of ultrasound-guided fine-needle aspiration biopsy in 124 complex nodules in 113 patients. This method proved to be highly effective, yielding a satisfactory specimen for cytological evaluation in 94% of the nodules, suggesting that it is an excellent modality for the evaluation of complex nodules and also for the reevaluation of those nodules with a nondiagnostic result on conventional fine-needle aspiration biopsy. (*J Clin Endocrinol Metab* 86: 4089–4091, 2001)

CYSTIC THYROID NODULES represent a major challenge for an adequate cytological diagnosis, yielding a high rate of nondiagnostic fine-needle aspiration biopsies (FNAB) attributable to scarcity or absence of follicular cells (1–5). For years, the diagnosis and treatment of cystic nodules have relied on simple aspiration of the fluid (6–9). The advent of high-resolution ultrasound has helped us to understand better the nature of these nodules, showing that most of the nodules initially considered to be cystic are actually complex lesions (solid-cystic) (10).

Ultrasound-guided FNAB (UG-FNAB) has emerged as an alternative to conventional FNAB (C-FNAB) for the diagnostic evaluation of nonpalpable nodules and for the repeat evaluation of nodules with previous nondiagnostic C-FNAB. It is also an excellent method for the evaluation of complex nodules by precisely positioning the needle in the solid portion of these nodules. However, no previous study has addressed the efficacy of UG-FNAB for the evaluation of complex nodules.

To determine the efficacy of UG-FNAB in the evaluation of complex nodules, we studied 113 patients with 124 complex nodules referred to our institution. The efficacy was determined by the number of satisfactory specimens obtained. We also evaluated the usefulness of UG-FNAB in previously unsuccessful C-FNAB. Furthermore, we compared UG-FNAB specimens with histological results in a subgroup of patients in whom thyroidectomy was performed at a later date.

Subjects and Methods

Study subjects

UG-FNAB is the preferred method in the evaluation of thyroid nodules at our institution. From July 1997 to July 2000, 509 patients were referred for this procedure and were studied prospectively. In 113 patients (25.3%), 129 nodules were classified as complex nodules (50% or more of the nodule filled with fluid). Five patients were lost to follow-up after the procedure and were not included in the analysis. Purely cystic nodules [no visible solid part; n = 25 (4.9%)] or solid nodules [absence or less than 50% fluid within the nodule; n = 355 (69.8%)] were excluded from the study.

Biopsy procedure

During the procedure, the patient was kept in the supine position with slight hyperextension of the neck. Local anesthetic was not routinely applied unless requested by the patient. Palpation of the nodule, UG-FNAB, and preliminary evaluation of the slides were performed by the same author for all patients (M.B.). A 7.5-megahertz probe was placed on the neck perpendicular to the thyroid, allowing clear visualization of the nodule. A 23- to 25-gauge needle was introduced next to the medial edge of the transducer, allowing visualization of the tip of the needle while it was guided to the biopsy site. Our initial approach was to perform a first biopsy with partial aspiration of the fluid, followed by a second biopsy of the solid part of the nodule (42 nodules). However, after a high rate of hemorrhage within the cavity of the nodule was observed after partial aspiration, it was decided not to aspirate the fluid and to proceed directly to biopsy the solid part of the nodule.

Once the needle was introduced into the solid part of the nodule, 3–5 ml of negative syringe pressure was applied. After aspiration, the smear was placed on slides and air-dried. One to three slides from each patient were stained with Wright-Giemsa stain to confirm the presence of follicular cells. If follicular cells were scanty or absent, the procedure was repeated until the number of cells was considered sufficient. The slides were subsequently stained with May-Grünwald-Giemsa stain. To evaluate the diagnostic yield from simple aspiration, the fluid from the first 42 samples in which fluid was aspirated was stained with Papanicolaou stain after cytospin cytocentrifugation.

Criteria for cytological diagnosis

The nodules were diagnosed as benign (abundant colloid and typical follicular cells), malignant (atypical follicular cells with malignant nuclear features), indeterminate (follicular and Hürthle cell neoplasms as well as specimens considered suspicious for malignancy), or nondiagnostic (fewer than six clusters of follicular cells visualized on at least two smears). Interpretation of the slides was performed by one of two experienced cytopathologists. A subgroup of 14 patients were referred for surgery, and the surgical pathology was compared with preoperative UG-FNAB.

Abbreviations: C-, Conventional; FNAB, fine-needle aspiration biopsy; UG-, ultrasound-guided.

Results

Patients characteristics

In 509 patients evaluated with UG-FNAB, 124 complex nodules were identified in 113 patients. The mean age of the patients was 41.8 ± 12.9 yr, and 107 patients were women. The majority of the nodules were located in the right lobe (58.1%). Eighty-nine percent of the patients were euthyroid at the time of the procedure, and the average longest diameter of the nodules was 2.4 ± 1.1 cm. The average number of passes for each nodule was 1.9 ± 0.9 (1 to 6). No complications were seen during the procedure.

Cytological analysis

In 117 of the 124 nodules, adequate number of cells were present for cytological diagnosis, yielding a diagnostic rate of 94.4%. Of these 117 nodules, 108 were benign and 2 were malignant. Results were indeterminate in 7 nodules (6 follicular neoplasm and 1 suspicious for malignancy). Follicular cells were scanty or absent (nondiagnostic aspirates) in the other 7 nodules.

Of the initial 42 nodules in which fluid aspiration was performed, 11 (26.2%) developed hemorrhage within the cystic part of the nodule soon after the aspiration. Analysis of the fluid obtained from these 42 nodules failed to show any follicular cells in 95% (n = 40) of these nodules. Scanty benign follicular cells were seen in 2 (5%) specimens. However, when the second biopsy of the solid part of these nodules was performed under UG-FNAB, the diagnostic accuracy was 95%.

Comparison of C-FNAB and UG-FNAB

Thirty-five of 124 nodules had been evaluated previously by C-FNAB (Fig. 1). Nine of these nodules had a previous nondiagnostic C-FNAB. Of these 9 nodules, 8 were diagnosed on UG-FNAB as colloid nodules, whereas 1 nodule yielded insufficient material for diagnosis (diagnostic rate of 91%). The remaining 26 were diagnosed previously on C-FNAB as benign colloid nodules. On UG-FNAB, 23 were confirmed to be benign colloid nodules, 1 was nondiagnostic, and 2 were diagnosed as indeterminate (follicular lesion) (one of these patients was referred for surgery, and the surgical pathology showed colloid goiter).

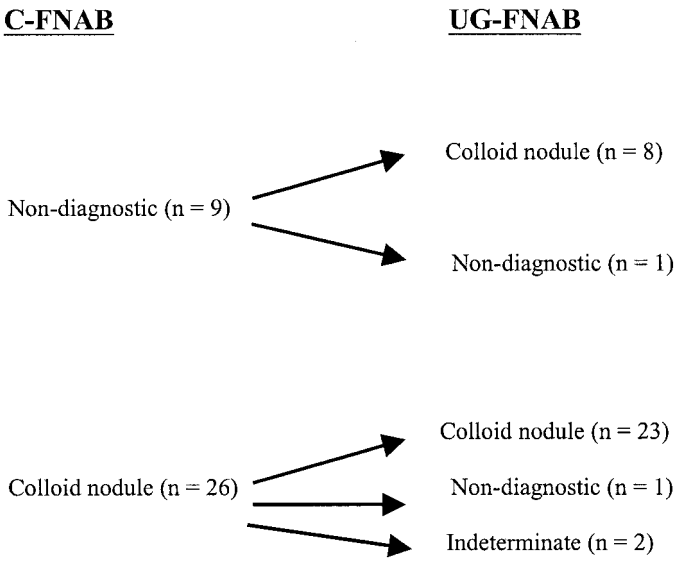

FIG. 1. Comparison of cytology results from C-FNAB and UG-FNAB. Numbers in *parentheses* represent the number of patients.

Comparison of surgical pathology and UG-FNAB

Fourteen patients (11.3%) were referred for surgery (Table 1). All patients with either a benign or a malignant diagnosis on UG-FNAB had confirmation of these cytological findings on surgical pathology. One patient with nondiagnostic cytology was found to have papillary carcinoma. Among four patients with indeterminate results (follicular neoplasm) on cytology, one had a benign colloid nodule, one had a follicular adenoma, one had a papillary carcinoma, and one had a follicular carcinoma. Considering indeterminate lesions as suspicious for malignancy (because these patients are referred for surgery), the sensitivity of UG-FNAB for complex nodules was 80%, the specificity was 77%, the positive predictive value was 66%, and the negative predictive value was 100%. Accuracy for the detection of malignancy was 85.7%.

Discussion

We have demonstrated that UG-FNAB is a highly effective method for the evaluation and biopsy of complex nodules with a high yield of satisfactory aspirates (94%) and also for the reevaluation of patients with a previous nondiagnostic C-FNAB. These data clearly suggest that complex nodules are better evaluated under ultrasound guidance.

For decades, simple aspiration of the fluid was the method of choice for the evaluation and treatment of cystic nodules, disregarding the fact that many of these nodules had a solid component. However, this procedure was associated with a low diagnostic accuracy (12–35%) (3, 7) and a high rate of fluid reaccumulation (8, 9). The high rate of acellular and nondiagnostic specimens in our study confirms the low diagnostic accuracy rate if simple aspiration is performed by C-FNAB.

The mechanism by which fluid collects within a nodule is unclear. Pure cystic nodules are lined by a monolayer of epithelial cells (8), which are probably responsible for the secretion of fluid. However, pure cystic nodules are rare and constitute only 3–4% of all thyroid nodules (2, 11). Complex nodules are thought to result from degeneration of solid nodules (8, 10, 12), with the accumulation of fluid probably resulting from intranodular necrosis and hemorrhage by

TABLE 1. Comparison of results from UG-FNAB cytology and surgical pathology

UG-FNAB cytology	Surgical pathology
Colloid goiter (7)	Colloid goiter (7)
Follicular neoplasm (4)	Colloid goiter (1), papillary carcinoma (1), follicular carcinoma (1), follicular adenoma (1)
Papillary carcinoma (2)	Papillary carcinoma (2)
Nondiagnostic (1)	Papillary carcinoma (1)

The numbers in *parentheses* represent the number of patients.

rupture of the fragile vascular network (7, 10, 13). This is supported by the observation of hemorrhage occurring soon after fluid aspiration, which probably occurs as a result of a sudden reduction in intranodular pressure (4). This may be the reason for the low recurrence rate of cystic nodules after percutaneous ethanol injection, which results in vascular thrombosis (14).

Complex nodules are considered to be among the main causes of nondiagnostic aspirates and diagnostic errors (11, 15) on C-FNAB due to three reasons. 1) Aspiration of the fluid alone may be considered to be adequate for cytological evaluation, especially if the residual nodule is not palpable after aspiration. In the present study, fluid analysis alone after simple aspiration failed to make a diagnosis in 95% of the patients. 2) By C-FNAB, the solid part of a complex nodule may be falsely considered by the physician to have been successfully biopsied if after complete aspiration of the fluid a residual nodule is palpable and biopsied (16). However, we demonstrated that hemorrhage was a frequent complication after fluid aspiration and, therefore, the palpable nodule may actually represent hemorrhage rather than the solid part of the nodule. Some authors have advocated applying pressure at the biopsy site for 5 min after aspiration of a cystic nodule (4, 8). However, this practice was later shown to be ineffective in preventing hemorrhage (17, 18). 3) Solid components of a complex nodule are not visible without ultrasound and may not be palpable. Therefore, there is no certainty that the solid part of the nodule has been biopsied with C-FNAB.

False-negative results attributable to either sampling errors or cytological misinterpretations are also mainly associated with complex nodules. Meko and Norton (19) found that 25% of the patients with false-negative results on C-FNAB had complex nodules compared with only 9% with solid nodules. Santos *et al.* (2) demonstrated that cystic nodules yielded insufficient material with C-FNAB more often than solid nodules (24 *vs.* 18%). In another study, false-negative results were significantly higher in cystic nodules (64%) compared with solid nodules (1.4%) in 263 nodules evaluated preoperatively by C-FNAB (20).

Malignancy rates among cystic nodules are reported to vary from 3 to 25% (2, 3, 5–7, 12, 21, 22). The inconsistency in these results may be attributable to lack of uniform criteria in defining these lesions and for surgical referral. Many authors report their data on cystic nodules based on fluid aspiration alone when they may actually be describing complex nodules. In our study, we found that 5 of 124 complex nodules (4%) were malignant.

Ultrasound guidance has been previously suggested to better evaluate complex nodules (2, 15, 23). Walfish *et al.* (24) reported the usefulness of ultrasound evaluation of thyroid nodules before C-FNAB. However, in that study, the nodules were not biopsied under direct ultrasound guidance. Giuffrida and Gharib (1) reported that a repeat C-FNAB of cystic nodules after an initial nondiagnostic result yielded specimens with a satisfaction rate of only 50%. Therefore, some authors recommend UG-FNAB for nodules with an initial nondiagnostic C-FNAB (2, 25). In this study, we demonstrated that UG-FNAB yielded a diagnostic accuracy of 91% in nodules with a previous nondiagnostic C-FNAB, hence confirming that UG-FNAB is the procedure of choice in the reevaluation of nondiagnostic complex nodules.

We conclude that UG-FNAB is an excellent initial diagnostic method for the evaluation of complex thyroid nodules and also for the reevaluation of complex nodules previously found to be nondiagnostic by C-FNAB. We propose that complex nodules originate from solid nodules and that UG-FNAB is the best method to make a definitive diagnosis.

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