LETTER / ENT

Management of thyroid nodules on US with benign or atypical cytological features

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The diagnosis of thyroid nodule is based on the ultrasound examination and TIRADS (Thyroid Imaging Reporting and Database System), which classifies the risk of malignancy according to ultrasound criteria [1]. This determines the management of the patient, the cornerstone of which is ultrasound-guided fine needle aspiration, which allows the thyroid nodule to be classified into one of six cytological categories associated with a risk of cancer and the diagnostic and therapeutic action to be taken according to the Bethesda reporting system of 2010 [2]. Highly suspicious TIRADS ultrasound signs must be strictly defined to avoid reducing the specificity and positive predictive value of the score.

TIRADS 2 and 3 nodules developing in a suspicious way on ultrasound

Some benign nodules, initially classified as stage 2 or 3 according to TIRADS, may be remodeled over time and later show suspect ultrasound characteristics (be strongly hypoechoic, a nodule taller than wide, the presence of microcalcifications, irregular margins), thus causing them to be classed as TIRADS stage 4B or 5 (Fig. 1).

Changes can be spontaneous or secondary to needle aspiration biopsy or percutaneous ethanol ablation treatment [3,4]. Cytological analysis can be ambiguous (particularly if classified as atypia of undetermined significance [AUS] according to the 2010 Bethesda system). In our experience, many suspect nodules (TIRADS 4B and TIRADS 5) are ultimately found to be benign (follow-up and successive cytology, pathological anatomy). In our opinion, certain features strongly suggest the benign nature of such nodules: some of them have a suspect part (irregular margins, hypoechoic, calcified) together with an echogenic part, sometimes in the form of a cyst, a vestige of the nodule that formerly appeared benign (Fig. 2). In this situation, volume reduction is frequent and no lymphadenopathy is seen in the drainage sites. Obviously fine needle aspiration is still indicated. If the cytological results include atypia of undetermined significance, in 50% of cases a second cytological sample will allow the nodule to be reclassified as benign. If the second result falls into the AUS category, diagnostic surgery is generally recommended. However, the distinctive ultrasound structure of the nodule and its modification over time can alert the radiologist and the cytologist to the possibility of a remodeled benign nodule and allow monitoring with another fine needle aspiration to be considered instead of surgery [5].

It is of major importance to compare current ultrasound images with the previous ones. A picture archiving and communication system is of great help to depict changes over time to reach the final diagnosis of remodeled benign nodule. Comparison of the cytological result (AUS) and the good quality archive image (an enlarged, optimized image) will give more precise clues for the diagnosis. Thus, a soft AUS nodule (elastography showing no stiffness gradient with the adjacent thyroid parenchyma) will be highly likely to be benign [6,7]. Conversely, finding highly suspicious ultrasound criteria (TIRADS 4B and TIRADS 5), excluding the particular case mentioned above of a nodule evolving towards necrosis, will more strongly suggest the possibility of a thyroid carcinoma [8,9].

Hyperfunctioning thyroid nodules posing diagnostic problems both in ultrasonography and cytology

When thyroid stimulating hormone (TSH) is low or low normal (<0.5 μu/mL), thyroid scintigraphy will generally show the benign nature of the hyperfixing (hot) nodule showing signs of hyperactivity that may give false positives for malignancy.

TIRADS 4 nodules, where the location or appearance leads to searching for molecular biology markers or measurement of thyroglobulin

The T1799A (V600E) mutation activator of the BRAF gene is the most common and specific oncogenic factor for papillary carcinoma, but its sensitivity is limited, somewhere between 45% and 50%. Where there are needle aspiration biopsy atypia (AUS), particularly in the cystic form with a small bell-like cavity or the follicular variant, the presence of this mutation in the control biopsy liquid indicates a probable papillary neoplasia and de facto requires surgery [10]. AFIRMA Thyroid FNA Analysis (AFIRMA), which allows the expression of 142 different genes to be studied, may also determine whether indeterminate cytology is or is not suspicious for cancer [11].

A micronodule located in the middle or upper third of the thyroid may lead to medullary thyroid carcinoma being suspected, particularly if it contains echogenic spots suggesting the presence of amyloid material and if the serum calcitonin titer is raised (sensitivity in the order of 98%) (Fig. 3).
Figure 1. A benign nodule evolving towards necrosis. An initially hyperechoic nodule with a small strongly hypoechoic peripheral portion (star) (A). Two years later, the poorly delimitated, hypoechoic part has increased (star) and has extended to the majority of the nodule (B). Needle aspiration cytology has shown the presence of cell atypia (AUS according to Bethesda) probably related to necrosis. Another follow-up ultrasound examination with a control needle aspiration biopsy shows that the nodule has remained stable in size with benign cytology. There is a vestigial echogenic portion of the nodule of previously benign appearance.

Figure 2. Spontaneous desiccation of a benign nodule, with suspect ultrasound characteristics on follow-up. Right thyroid nodule (arrow), completely encysted, measuring 20 mm in its longest axis, classed as TIRADS 2 (A). Nine months later, the same nodule had suspect ultrasound characteristics (calcifications, was markedly hypoechoic and had irregular margins) which meant that it was classed as TIRADS 5 (B) but had greatly decreased in size (measuring 7 mm). The needle aspiration biopsy performed and later follow-up concluded that the nodule was benign.

In the case of microcarcinoma, the increase in serum thyrocalcitonin may nevertheless be very limited (15–100 pg/mL) and needle aspiration cytology remains ambiguous (AUS). In addition, concomitant use of proton pump inhibitors (PPI) and a patient who smokes may result in false positive laboratory results. In certain cases, measuring the thyrocalcitonin in the rinsing liquid will permit diagnosis by showing a very high concentration of it in situ, allowing early and appropriate surgery [12]. This measurement should thus be proposed in the following situations: a hypoechoic nodule the volume of which has been shown to be increasing and the initial cytology of which was indeterminate, having amorphous echogenic deposits (suggesting amyloid material) and serum calcitonin levels which are not conclusive but suspect (<100 pg/mL with the kinetics not falling after stopping PPIs and tobacco), particularly if there is a family history of MEN type 2.

In conclusion, precise ultrasound analysis of the nodule and its evolution over time, and the necessary comparison of imaging results and cytological findings limit the risks of false negatives and false positives of needle aspiration cytology. Ultrasound monitoring of a suspect thyroid nodule...
with repeat needle aspiration biopsy if the cytology is benign or AUS, measurement of thyrocalcitonin concentration and looking for genetic markers in certain selected cases should improve the already good diagnostic performance of the radiologist/cytologist team.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

References


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