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Review / Derleme

Current approach to thyroid nodules: the Bethesda classification

Tiroit nodüllerine güncel yaklaşım: Bethesda sınıflaması

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ABSTRACT

The first approach to evaluated of thyroid nodules is usually fine needle aspiration biopsy. Assessment of this easy applied method is definitely significant. In order to reporting of fine needle aspiration biopsy, the clinician understands disease should be the similar as the cytopathologists means disease. There are several concepts revealed by some commission for this aim. This study emphasized the algorithms easing the pathologists-clinician correlation and especially Thyroid Bethesda reporting system.

Keywords: Fine needle biopsy, thyroid nodule, clinician-patologist communication

ÖZ

Tiroit nodüllerinin değerlendirilmesinde ilk yaklaşım genellikle ince iğne aspirasyon biyopsisidir. Bu kolay uygulanan yöntemin değerlendirilmesi kesinlikle çok önemlidir. İnce iğne aspirasyon biyopsisinin bildirilmesinde klinisyenin anladığı hastalık ile sitopatoloğun belirttiği hastalığın benzer olması gerekmektedir. Bu amaç için birtakım komisyonlar tarafından ortaya konan birkaç konseptler vardır. Bu çalışma, patolog-klinisyen korelasyonunu kolaylaştıran algoritmaları ve özellikle de tiroit Bethesda raporlama sistemini vurgulamıştır.

Anahtar Kelimeler: Tiroit nodülü, ince iğne biyopsisi, sitopatolog-klinisyen iletişimi

INTRODUCTION

Thyroid is among the bigest endocrine glands and that can be easily examined and biopsied because it is superficially located (1). In our country, there are endemic goitre zones like the black sea (1). History physical examination, thyroid antibodies and radiological examinations are not sufficient for the preoperative identification, although the nodules of thyroid are usually not malign. Thyroid fine needle aspiration biopsy (FNA) was first applied by Ellis and Martin in the United States in 1930 (2). In the 1950s, it began to be widely used in Scandinavian countries, especially in Sweden, and it has been widely used all over the world in the last 20 years (2).

Nodules of thyroid are a separate lesion in the tissue of thyroid which different from the thyroid parenchyma with ultrasonography. Nodules of thyroid are detected in 50% -60% of healthy humans. In epidemiological studies, the thyroid nodules prevalence is reported to be approximately 1% in male and 5% in female (3). The main clinical problem in thyroid nodules is to exclude malignancies in these nodules. The annual of thyroid malignancies incidence increased from % 0049 to % 0.0143 between 1975 and

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2009 in the United States (4).

Two major guidelines for approach to thyroid nodules are being followed as a major source all over the world in order to prevent over-treatment from low-risk patients in terms of thyroid malignancy and to prevent inadequate follow-up and treatment of high-risk illnesses. These guidelines which will be mentioned in the following; The American Thyroid Association (ATA), the Association of American Clinical Endocrinologist (AACE), the College of American Endocrinology (ACE), and the Associazione Medici Endocrinologi (AME) guidelines.

Thyroid ultrasonography (US) is commonly used to assessment the risk of malignancy in the nodules of thyroid for deciding whether the FNA is suspected or not (5). In the US study, although sensitivity is low for a single feature, the most specific thyroid cancer features are microcalcifications, irregular edges and tall size form (6). When we look at the features of follicular thyroid carcinoma, it is a round nodule with hyperechoic, intranodular vascularity, without calcification (9). It is not appropriate to estimate malignancy with US specifics only because these features described in the US have low predictive sensitivity to cancer (7).

FNA is the best appropriate procedure for the assessment of thyroid lesions in the presence of clinical symptom. In the FNA guided by the US, both diagnostic accuracy and false negative cytology rates were found to be lower than FNA with palpation (8). For this reason, US guidanced FNA should be preferred for nodules with a non-diagnostic cytology (nodules with > 25% -50% cystic contents) or sampling error (nodules with non-palpable or posteriorly located) (8). Larger nodules over than 1 cm with moderate and high US findings and in nodules larger than 1.5 cm with a low degree of suspicious US findings diagnostic FNA are in recommended. In nodules with very low-suspicious US findings, diagnostic FNA may be considered when the largest size is greater than 2 cm. In this group < 5 mm nodules are more suitable to follow US instead of FNA. FNAs are not required for nodules that are completely cystic and do not meet the above criteria (9).

Education and License

The most important diagnostic problem in FNA is inadequate material. Therefore, it is emphasized that sufficient training is necessary in taking and preparing samples. Studies show that the thyroid FNA results are better which obtained by the same person prepared and reported. FNA should be reported by an educated hand and experienced cytopathologist (10).

Technical

27-25 gauge needles are enough small and not to cause pain and bleeding, they enlarge to take samples. This process can also be used in USG mode. Local anesthesia is usually not necessary. Optimal preperation for routine examination, Papanicolaou staining suitable for alcoholics, Romanowsky (Wright-Geimsa stainings) for airborne spreads (Figure 1, 2). A cell block can be made if the cyst fluid contains fibrin or small tissue particles (10). If the review can not be done immediately; the material can be collected in saline solution for cytospin, formol for cell block, liquid-based collections for liquid-based examination (Surepath, ThinPrep). Factors affecting sample adequacy in solid or cystic lesions; the experience of the aspirator, the nodule structure (location, size, localization, cystic component, fibrosis), the needle diameter, the number of interventions, Sufficiently, the minimum criterion is 5-6 tyrosit groups, each of which has at least 10 cells (10,11).

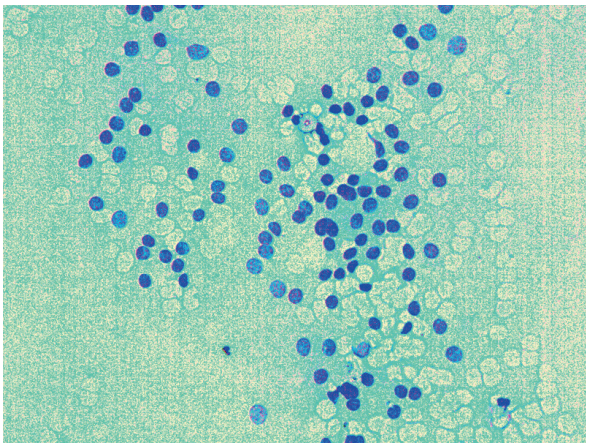

Figure 1. A thyroid aspiration biopsy reported as benign cytology according to the Bethesda system (Papanicolau, X200)

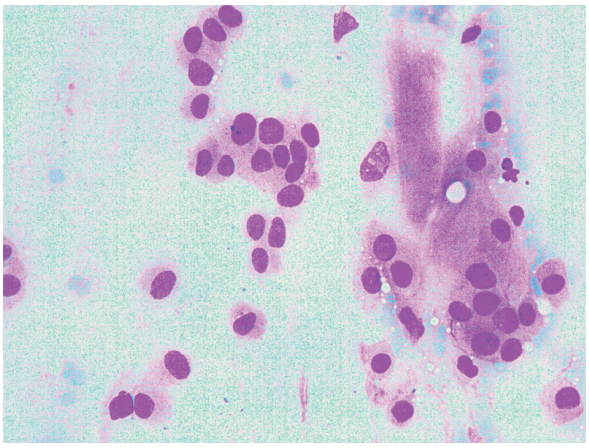

Figure 2. A thyroid aspiration biopsy reported as benign cytology according to the Bethesda system (May-Grünwald Giemsa, X200)

Table 1. Thyroid FNA classification scheme of the various communities.

Papanicolaou Society of Cytopathology, 1997	1-Inadequate / Not optimal 2-Benign 3-Atypical cell presence 4-Malignity suspected 5-Malignant
American Thyroid Association, 2006	1-Inadequate / Not optimal 2-Malignant 3-Undetermined 4-Neoplasia suspected 5-Carcinoma suspected
Association of American Clinical Endocrinologist & Association Medici Endocrinologi, 2006	1-Benign 2-Malignity doubt 3-Follicular Neoplasm 4-Non-diagnostic / USG suspect

TERMINOLOGY AND MORPHOLOGICAL CRITERIA

FNA is a useful method for evaluating of the thyroid nodule. The main aims are to supply a rational direction in disease management, to determine the requirement of surgery and suitable surgical method. There is currently no standard for thyroid FNA reporting. Several authors have proposed a few classification systems (Table 1), in the light of personal / institutional experience and some clinical organizations, suggesting that there is a discrepancy in the diagnostic terminology perception between clinicians and pathologists (10,11). Numerous studies have established a sequential scheme of multiple diagnostic categories (benign, undefined lesion, follicular neoplasm, suspicious, malignant and inadequate) for thyroid FNA classification. A system that allows for the identification of the malignancy risk and its ability to be expressed clearly can be regarded as optimal (10,11). Recently, it has started to use a new system called "Bethesda Reporting System" and its usage is getting widespread.

BETHESDA REPORTİNG SYSTEM

This system reported of FNAs in 6 categories. The main purpose of this system is that the clinician can adequately comment on the benign / malign potential of the disease. It was also aimed to use a common language and minimize pathologist-clinician incompatibility (11).

1. Non-diagnostic

There may be a few reasons for this. The most important of these are; biopsy should not be done from the correct place, not taken with the right technique, rules are not followed when preparing preparter. However, the most important point here is that non-diagnostic cytology reports are not interpreted in favor of benign disease. This thyroid nodule should be treated as similar as no procedure has been performed (11).

2. Benign

This group includes neoplastic and non-neoplastic lesions such as nodular / diffuse goitre, chronic lymphocytic thyroid, hyperplastic / adenomatoid nodule. These patients are followed by radiological and clinical examination in periodic times (11) (Figure 1).

3. Undetermined Atypia Significance

This identification is a heterogeneous group consisting of benign or follicular neoplasm not classified as neoplasia. Findings are not convincing to interpret as benign. Fertility and structural atypia are not adequate for the explication of "follicular neoplasia" or "malignancy suspicion". A little of cases are due to reasons such as low cellularity, poor fixation, blood clotting. Malignant risk is between 5 – 10%. In this group, recurrent FNA and clinical / radiological correlations may be required. This optional category is required to be at least in the thyroid FNA reports (11).

4. Follicular Neoplasm / Follicular Neoplasm Suspected

The risk of malignancy is low or in the intermedia group (20 % - 30 %). This group includes follicular-patterned lesions with non-papillary and cellular lesions. Most of the researches on the subject indicate that the lesions that are diagnosed as such are more than 20% more likely to find malignancy in the surgical materials, and that this ratio is even higher in cell lesions and nodule diameters of 3.5 cm or more. Other descriptive concepts used for this group are, follicular lesion reminiscent of neoplasm and microfollicular proliferation. The majority of the patients undergo lobectomy / hemithyroidectomy with this results and a definitive diagnosis is made by histopathological examination describing the lesion (11).

'Follicular neoplasm suspected' is a different term that is alternatively suggested and acceptable. This definition includes both malignant and benign lesions; follicular adenoma / carcinoma, h***ürthle cell adenoma / carcinoma. This terminology also identifies the limits of thyroid cytology. That is, follicular carcinoma*** of thyroid must be diagnosed only by the appearance of vascular and / or capsular invasion. In the excisional material, only 20 - 30% of the cases are reported as follicular carcinoma, the back are cellular adenomatoid nodules or follicular

adenomas, and a few are reported as follicular variant of papillary thyroid cancer (11)

5. Malignity Suspected

In these cases, consultation during operation (frozen section or intraoperative cytology) is recommended. The following terms can be used in this definition as suspected of papillary carcinoma; the most of cases in this category (50% - 75%) are reported as follicular variants of papillary thyroid carcinoma. Suspected of medullary carcinoma; this cytological diagnosis should be used in situations where there is no specimen that will permit immunofluorescence with calcitonin. Diagnosis should be supported by looking at the level of serum calcitonin. Suspecting lymphoma, reaspiration is recommended for flow cytometry studies. Metastatic / secondary thyroid tumor is suspected; in the presence of total necrosis of lesion cells, anaplastic carcinoma should be kept in mind (11).

6. Malign

Malignant thyroid lesions are categorized as cytologically papillary carcinoma, anaplastic carcinoma, medullary carcinoma, malignant lymphoid neoplasia and metastases (11) (Figure 2).

CYTOLOGY INTERPRETATION IN THYROID NODULES

ATA guidelines refer to non-diagnostic FNAs in the first group; US guidance again recommends FNA, if there is no high suspicion in the US for non-diagnosed nodules despite recurrent FNA, surgery is recommended in the presence of close follow-up or clinical and radiological risk factors. It is suggest that the FNA should not be made again within 3 months after the first FNA to avoid false positive diagnosis in ATA guidelines (12,13).

In the second group of patients, i.e, nodules with benign cytology, no other diagnostic applications or treatment approaches are required. When the nodules with benign cytology are examined in the literature, the malignancy strictly maintains uncertainty of excretion in > 4 cm nodules. Guidelines for patients with benign FNA and high suspicion of US nodules suggest follow-up US and FNA. If the size of the nodules increases or new suspicious nodule formation is detected, FNA should be performed again. US follow-up is not necessary in patients with FNA twice and patients with benign cytological results (12,13).

Patients in the third group included a group of patients that the decision was rather complex. ATA guidelines recommend repeat molecular testing or FNA to support follow-up or the risk of malignancy evaluation after reassessment of sonographic and clinical characteristics for these lesions. It is also stated that follow-up surgery may be performed depending on clinical risk elements, sonographic characteristics and the preference of patients (12,13).

Although ATA guides recommend surgical excision for disease diagnosis in the fourth group, molecular tests can be used to evaluate malignancy risk after clinical and sonographic evaluation, and in cases where molecular testing is not performed, it is indicated that surgeon is preferred option (12,13). .

ATA guidelines refer to surgical treatment for the fifth group of the Bethesda system with clinical risk elements, sonographic characteristics, patient priority, and molecular test results (12,13).

In patients with cytology in the sixth group, ATA guidelines usually refer to surgical treatment. Despite the malignant cytology, the cases in which surgical treatment may be postponed can be listed as follows; papillary microcarcinomas, patients with advanced surgical risk, patients with relatively short prognosis, patients with other surgical or medical conditions that should be prioritized from the surgeon (12,13). The following is a summary of the malignancy expectation in thyroid cytopathologic diagnoses (Table 2).

Table 2. Evaluation systems for ATA and AACE / ACE / AME in thyroid cytopathologies

ATA	AACE/ACE/AME	Description	Expected malignancy risk (%)
Bethesda 1	Thyroid cytology 1	Non-diagnostic	1-5
Bethesda 2	Thyroid cytology 2	Benign cytology	0-5
Bethesda 3	Thyroid cytology 3	Atypia of undetermined significance	5-15
Bethesda 4	Thyroid cytology 3	Follicular neoplazm	15-30
Bethesda 5	Thyroid cytology 4	Malignity suspected	65-75
Bethesda 6	Thyroid cytology 5	Malign cytology	98-99

RESULT

It is very important to act according to internationally accepted guidelines and to pay attention to cytopathologist-clinician correlation in approaching thyroid nodules. If these diagnoses are understood and used correctly, patients will be freed from recurrent biopsies, patients will be diagnosed early and surgical treatment will be done without delay. Cytopathologist-clinician communication with specific algorithms contributes to this topic, and the clinician will also benefit from the feedback of the pathologist.

DECLARATION OF CONFLICTING INTERESTS

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

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