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FINE NEEDLE ASPIRATION OF THE THYROID

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SUMMARY – Fine needle aspiration (FNA) of the thyroid has been utilized as a diagnostic method for 40 years. The main purpose of thyroid FNA is to differentiate nodules that require surgery from those that do not. The sensitivity of thyroid FNA ranges from 65% to 99%, and its specificity from 72% to 100%. Ultrasound-guided FNA of the thyroid is recommended, especially for sampling of a small, deep nodule. One to four aspirations suffice in single nodular lesions measuring less than 3 cm in diameter. Although the criteria used to establish specimen adequacy are somewhat controversial, most institutions require the presence of follicular cells. FNA diagnosis of thyroid disease is a clinicocytologic diagnosis, and correlation with clinical findings is mandatory for success. At our institution, diagnostic FNA lesions are subdivided into the following general diagnostic categories: benign, indeterminate, and malignant. Benign lesions include lesions with the diagnosis of benign thyroid nodule, nodular goiter, and thyroiditis. Indeterminate lesions include cellular follicular lesion, follicular neoplasm and Hürthle cell neoplasm. Malignant neoplasms include papillary carcinoma, high-grade follicular carcinoma, medullary carcinoma, anaplastic carcinoma, large cell lymphoma, and metastatic carcinoma. No clinical or laboratory test is sensitive and specific enough to distinguish reliably whether a follicular neoplasm identified on FNA is benign or malignant. This position may be changed with the development of molecular approaches to the diagnosis. CD44v6 and galectin-3 seem to be most promising tumor markers for thyroid malignancies of follicular epithelial cell origin.

Key words: *Thyroid diseases, pathology; Thyroid neoplasms, pathology; Biopsy, needle; Cytodiagnosis*

Introduction

Fine needle aspiration (FNA) of the thyroid has been utilized as a diagnostic method for 40 years. The method was introduced by Söderström in 1952, has been extensively used in Sweden and shown to be both dependable and accurate[1]. However, the technique did not become well accepted in the United States until the late 1970s[2]. In Croatia, first experiences were reported in 1960s[3,4]. The Swedish pioneers used air-dried smears usually stained with May-Grünwald-Giemsa stain. In the United States, alcohol-fixed material and either Papanicolaou or hematoxylin and eosin stains have been used. Prior to the use of FNA, surgical excision of any remote suspicious lesion was the norm. Since the introduction of this method, the number of surgical procedures on the thyroid has been reduced by 48% and the percentage of cancers in the surgical material has risen from 11.5% to 43%[5]. Currently, FNA of the thyroid has become the first-line diagnostic technique in the evaluation of thyroid nodules, which is used in conjunction with other modalities such as ultrasonography, radionuclide scanning, and biochemical and antibody measurements as clinically indicated.

Clinically palpable thyroid nodules are exceedingly common, with a number of different studies indicating an annual incidence rate ranging from 4% to 8%[6-13]. Overall, there is a 10% life expectancy of developing a thyroid nodule[14]. Therefore, thyroid nodules are one of the com-

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monest medical problems that physicians encounter. The concern for both patients with thyroid nodules and their physicians is the risk of malignancy. However, only a small fraction of these lesions are caused by malignancy.

Although it appears that the incidence rate of thyroid carcinoma may be slowly increasing, it is low, with annual rates of only 25-40 *per* million population[6,9,10,15]. Together, all the variants of thyroid carcinoma account for only 1% of all new cancers[7]. Therefore, the vast majority of palpable nodules are entirely benign, and only approximately 5% represent cancer[16-18]. The clinician's fundamental goal is distinguishing the many benign from the few malignant nodules. Ideally, surgical management would be offered only to those thyroid nodule patients harboring malignancies, and all other patients would be managed more appropriately by conservative medical treatment.

The main purpose of thyroid FNA is to differentiate nodules that require surgery from those that do not. In experienced hands, it is also diagnostic for certain thyroid lesions, such as classic nodular goiter, Hashimoto's thyroiditis, papillary carcinoma, high-grade follicular carcinoma, medullary carcinoma, anaplastic carcinoma, large cell lymphoma, and metastatic carcinoma.

However, FNA of the thyroid does not eliminate all diagnostic operations. No test that serves a triage function is 100% effective, and the patient should be fully informed about the risk/benefit ratio of the procedure. The sensitivity of thyroid FNA ranges from 65% to 99%, and its specificity from 72% to 100%[12,19-22]. The reported false-negative rate ranges from 1% to 11%[20,22-24]. A false-positive report in thyroid cytology is not of major concern because, without this test, many more patients with solitary, 'cold' nodules would require excision for diagnosis. It is more important to maintain the lowest false-negative rate possible to ensure that few carcinomas will be missed. The aim is to achieve a false-negative rate of less than 2% and a false-positive rate of less than 3%[22,24-30]. The incidence of false-negative diagnosis is difficult to gauge because only approximately 10% of patients with benign cytologic findings undergo surgery[22]. A false-negative diagnosis is defined as a diagnosis of non-neoplastic lesion, which does not normally require surgery, rendered on a malignant lesion. A false-positive cytologic diagnosis is a diagnosis of neoplasm, which requires surgery, rendered on a non-neoplastic lesion. The false-negative rate is computed as the number of false-negative diagnoses divided by the total number of FNAs in the series x100. A false-positive rate is computed as the number of false-positive diagnoses divided by the total number of FNAs in the series x100[27].

Overall, FNA of the thyroid has resulted in a decrease in the cost of medical care in thyroid disease. The interpretation of the cytologic material from the thyroid is by no means simple. Except in some obvious situations, the identification of diagnostic cell patterns is difficult and requires excellent material and a great deal of experience.

Targets of Aspiration Biopsy

The principal indication for FNA of the thyroid is a solitary thyroid nodule. A classic multinodular gland is rarely suspicious for carcinoma[31]. It is a long-standing goiter with little or no progression in growth in a patient without previous irradiation to the neck[32]. In multinodular glands, the presence of a nodule that has grown rapidly, become distinctly larger or dominant, or changed in texture or consistency warrants FNA[33,34]. Recent study shows that the incidence of cancer is similar in those with clinically apparent solitary and multiple nodules[35]. In those with true solitary nodule confirmed at the operation, the risk of cancer is the same as in those with multinodular goiters[36]. FNA is also useful in patients with Hashimoto's thyroiditis because not only Hashimoto's thyroiditis can present as a solitary nodule but it can also coexist with thyroid carcinoma or lymphoma.

FNA Technique

Thyroid FNA need not be restricted to specialized centers; it can be performed effectively in a general hospital setting, outpatient department, or free-standing clinic. The individual who performs the aspiration must have proper training in the method. Although considerable experience is required to obtain adequate material with consistency, it is the intensity of experience rather than the duration of FNA practice that is important[25]. It is thought that examination of 30 to 40 FNAs annually should be required to maintain interpretative proficiency[12,37-39].

Preparation of the Patient

The patient should be placed in supine position with the neck extended; a pillow placed under the shoulders is

helpful. Reviewing the procedure with the patient prior to the aspiration usually appeases anxiety. The patient should be advised not to swallow or talk during the procedure because movement of the gland during aspiration may cause tissue tear and result in the formation of a hematoma.

Ultrasound-guided FNA of the thyroid is recommended, especially for sampling of a small, deep nodule or solid remnant of a cystic lesion[40].

If FNA of the thyroid is performed without ultrasound guidance, the entire thyroid should be palpated to determine the size and location of any abnormalities. The area should be cleansed with alcohol. Local anesthesia is not necessary. In patients who are very anxious topical freezing anesthetics (or even an ice cube) may be used.

Aspiration Procedure

Use of a 25-gauge needle with disposable 10-cc syringe is recommended for obtaining thyroid samples[41,42]. Drawing approximately 1-cc of air into the syringe prior to the aspiration will facilitate expelling the specimen after the procedure. During the puncture, the patient should remain immobile. Aspiration must be performed competently and rapidly; otherwise, blood may enter the needle and the syringe, making the material worthless. For cystic lesions, a larger caliber, 23-gauge needle with 20-cc syringe, may be used to evacuate as much of the fluid content as possible. The slides for wet-fixation should immediately be placed in alcohol or spray-fixed for Papanicolaou or hematoxylin and eosin staining. Air-dried slides are left unfixed until staining with May-Grünwald-Giemsa stain.

The number of aspirations made in each patient depends on the nature of the lesion. Generally speaking, one to four aspirations suffice in single nodular lesions measuring less than 3 cm in diameter. When the lesion is larger, as many as six aspirations may be required. The FNA procedure should be repeated for cases with inadequate yields, because repeating the aspiration provides an adequate diagnostic sample in as much as 50% to 88% of the initially unsatisfactory cases[35,43,44].

Specimen Adequacy

The cytopathologist has a responsibility to recognize when a specimen is inadequate for interpretation and to communicate this to the clinician. Although the need for obtaining adequate samples is unquestioned, issues regarding the criteria used to establish specimen adequacy are somewhat controversial. Most institutions require the presence of follicular epithelial cells[45]. Everyone agrees that any aspirate from a palpable nodule that contains neither colloid nor epithelial cells is inadequate and should be repeated[45,46].

The cellularity of a specimen, however, is greatly influenced by the intrinsic nature of the lesion from which the specimen was obtained. Many cases of benign colloid goiter yield abundant colloid but few follicular cells. In such cases, a diagnosis of 'consistent with colloid goiter' is acceptable, with the report containing a qualifier stating that the cytologic interpretation is limited by the paucity of follicular cells. Similarly, a cystic lesion that yields numerous macrophages with scant or no follicular cells may be reported as 'consistent with benign thyroid cyst', with the qualifier indicating that the interpretation is limited by the paucity or lack of follicular cells. In case of hemorrhagic cyst larger than 4 cm in diameter, the likelihood of malignancy is higher, and repeat aspiration is advised[47].

If the criteria for FNA specimen adequacy are too liberal, too many false-negative diagnoses will result; conversely, excessively narrow criteria will result in undue patient anxiety, many repeat aspirations, or unnecessary surgical excisions. If malignant cells, irrespective of the number, are identified in an aspirate, it should automatically be considered satisfactory. If too few malignant cells are present for a definite diagnosis, a 'suspicious' diagnosis or repeat aspiration may be suggested[46].

An acceptable rate of inadequate specimens is less than 15%[46]. No diagnosis should be rendered on inadequate or unsatisfactory specimens.

Cytopathologic Reports

The written cytologic report should be clear, concise, and clinically relevant. It is important to integrate clinical information with cellular interpretation. An exact cytologic diagnosis cannot be made only by observation of the cells. The experience of the cytopathologist in weighing clinical information helps manage the examination of the specimen, but the cells are still the crux of the matter. The cytopathologist must be able to balance clinical bias with microscopic examination. However, if the microscopic material does not support the diagnosis, one should

not make that diagnosis despite heavy clinical bias. Any diagnosis made must be defensible to peer review.

Diagnostic Groups

FNA diagnosis of thyroid disease is a clinicocytologic diagnosis, and correlation with clinical findings is mandatory for success[48]. There is no consensus as to exact format and style of reporting the results of FNA. In our institution, we subdivide diagnostic FNA lesions into the following general diagnostic categories: benign, indeterminate, and malignant (Table 1).

Table 1. Cytopathologic diagnoses

Benign lesions	Benign thyroid nodule
	Nodular goiter
	Thyroiditis
Indeterminate lesions	Cellular follicular lesion
	Follicular neoplasm
	Hürthle cell neoplasm
Malignant neoplasms	Papillary carcinoma
	High-grade follicular carcinoma
	Medullary carcinoma
	Anaplastic carcinoma
	Large cell lymphoma
	Metastatic carcinoma

Benign lesions

This group includes lesions with the diagnosis of benign thyroid nodule, nodular goiter, and thyroiditis. Whenever possible, a specific cytohistologic diagnosis should be provided. For example, Hashimoto's and DeQuervain's thyroiditis, colloid cyst and many nodular goiters can be diagnosed with confidence and accuracy.

Lesions in this group can be managed conservatively. If the nodules continue to enlarge, or fail to respond to suppressive thyroxine therapy, then repeat aspiration or surgical excision is indicated.

Indeterminate lesions

The definition of 'indeterminate lesion' is based on the fact that what determines the need for surgery is the diagnosis of a neoplastic *versus* non-neoplastic lesion. These lesions pose the greatest diagnostic difficulty for cytopathologist because there is substantial overlap in cytologic features of benign non-neoplastic lesions and well-differentiated follicular neoplasms (benign and malignant)[49,50].

The three cytologic categories that are recognized are cellular follicular lesion, follicular neoplasm and Hürthle cell neoplasm.

Cellular follicular lesion is best described as 'probably neoplastic'. This group includes adenomatoid nodule, nodule with Hürthle cell hyperplasia in Hashimoto's thyroiditis, follicular adenoma, and Hürthle cell adenoma. Hürthle cell carcinoma, a well-differentiated follicular carcinoma, and some cases of the follicular variant of papillary carcinoma are very rare exceptions but cannot be excluded. FNAs show relatively abundant, slightly atypical, follicular (or Hürthle) cells and scant colloid. It should be reported as 'cellular follicular lesion', with an added comment outlining the differential diagnosis for each individual case.

When the diagnosis of 'cellular follicular lesion' is made, and the patient is also judged to be at low risk, conservative medical management with follow-up monitoring is advised. Factors that contribute to a low index of suspicion of thyroid cancer include soft or cystic lesions, 'hot' nodules on radioisotope scan, and lesions that regress during thyroxine suppression. High-risk factors for cancer include age (>60 yrs), male sex, large size (>4 cm), rapidity of growth, rock hard texture of nodule, vocal cord paralysis, previous exposure to radiation, family history of medullary thyroid cancer, and growth during adequate thyroxine suppression.

Follicular neoplasm is best described as 'probably malignant'. It includes follicular adenoma and follicular carcinoma. Irregular microfollicles with nuclear overlap and central, dense colloid, in association with cytologic nuclear atypia, characterize follicular neoplasms[42] (Fig. 1). The determination of whether a follicular tumor is benign or malignant is based on tissue architectural features of capsular or vascular invasion, not cytomorphologic criteria alone[51-53]. A cytologic diagnosis of follicular neoplasm is an indication for surgical intervention, because this diagnosis implies that a well-differentiated carcinoma is not excluded on the basis of cytologic examination.

Hürthle cell neoplasm includes both Hürthle cell adenoma and Hürthle cell carcinoma. Their biologic behavior and the rationale for considering them as a distinctive clinicopathologic entity are debated[53-56]. However, the frequency of malignant transformation and the biologic aggressiveness of Hürthle cell tumors are superior to those observed in other differentiated follicular tumors[53,54]. They are indistinguishable from one another on the ba-

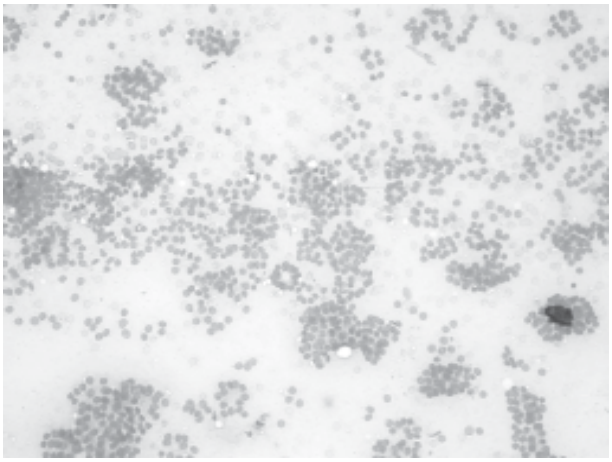

Fig. 1. *FNA of well-differentiated follicular carcinoma. Numerous acini, slightly enlarged nuclei with mild anisonucleosis (May-Grünwald-Giemsa stain, x200).*

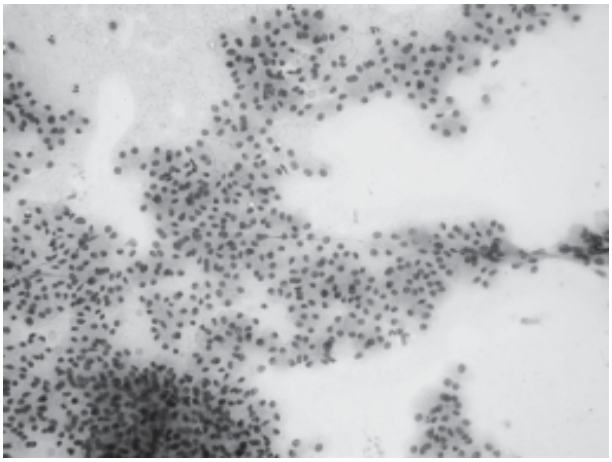

Fig. 2. *FNA of Hürthle cell carcinoma. Monomorphic cells with abundant, fine granular cytoplasm (May-Grünwald-Giemsa stain, x200).*

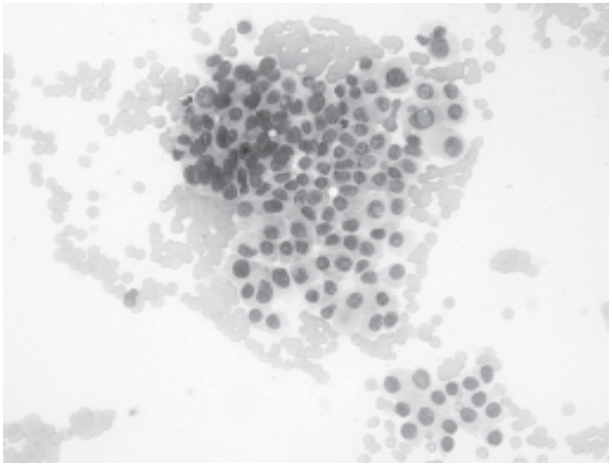

Fig. 3. *FNA of papillary carcinoma. Enlarged cells with dense cytoplasm, finely granular 'powdery' chromatin, and intranuclear cytoplasmic inclusions (May-Grünwald-Giemsa stain, x400).*

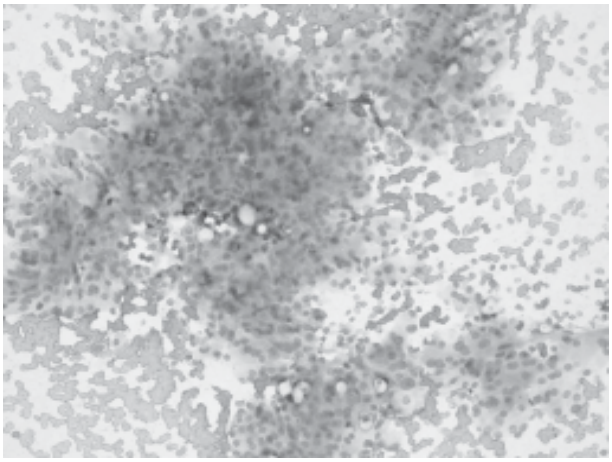

Fig. 4. *FNA of high-grade follicular carcinoma. Syncytial pattern with crowding, and overlapping of irregular nuclei (May-Grünwald-Giemsa stain, x200).*

sis of cytologic examination because the criteria for malignancy are based on the same architectural characteristics as for follicular carcinomas. Aspirates are monomorphic, highly cellular with cells that show little cohesiveness, and have characteristic abundant, granular cytoplasm with well-defined margins (Fig. 2). If FNA shows exclusively Hürthle cells without background of thyroiditis, the nodule should be surgically removed.

It is important to keep in mind that certain non-thyroid lesions in the neck, such as parathyroid adenoma and carotid body paraganglioma, may show a follicular cytologic pattern of FNA. If these are considered as diagnostic possibilities, immunoperoxidase staining for thyroglobulin and chromogranin may be helpful to resolve the diagnostic problem.

Malignant neoplasms

This group includes any specimen in which an unequivocal diagnosis of malignancy can be made. More common diagnoses are papillary carcinoma, high-grade follicular carcinoma, medullary carcinoma, anaplastic carcinoma, large cell lymphoma, and metastatic carcinoma.

Papillary carcinomas are usually diagnosed readily by FNA cytology. Characteristic findings include papillary tissue fragments composed of enlarged cells with dense cytoplasm, overlapping nuclei, finely granular 'powdery'

chromatin, nucleoli, nuclear grooves, and intranuclear cytoplasmic inclusions (Fig. 3). Psammoma bodies, dense sticky colloid, and multinucleated giant cells may also be present. When most of these criteria are met, the diagnosis poses little difficulty.

In high-grade follicular carcinomas, the nuclear contour is less smooth, the chromatin tends to have an irregular pattern, and the large nucleoli are often prominent (Fig. 4). Cells are arranged in irregular microfollicles with crowding, and overlapping of nuclei.

Medullary carcinomas are unusual tumors that arise from calcitonin-secreting C cells of the thyroid. The cytomorphologic features are very characteristic. The tumor cells occur singly or in loose monolayers. The cells are round, oval, polygonal, triangular, or spindle, and have abundant cytoplasm with red neurosecretory granules (Fig. 5). Cells contain round or oval eccentric nuclei with coarsely granular chromatin and small nucleoli.

The cytologic features of anaplastic carcinomas in smears are highly specific and easy to recognize. Undifferentiated, highly malignant cells show anisocytosis, anisonucleosis, irregular, bizarre hyperchromatic nuclei, numerous frequently pathologic mitoses, inflammation, and necrosis (Fig. 6).

Primary lymphomas of the thyroid are of B-cell phenotype, usually arising in a setting of Hashimoto's thyroiditis. The aspiration specimen lacks epithelial cell clusters, and consists of monomorphic population of lymphoid cells that are dispersed or sometimes arranged into lymphoid tissue fragments. Nuclei of the tumor cells are uniform, and occupy most of the cytoplasm. Nuclear details vary according to the type of lymphoma.

The majority of thyroid metastases are produced by contiguous spread of primary neoplasms of the pharynx, larynx, and upper third of the esophagus. The thyroid is subject to hematogenous disseminated disease in the advanced stages of carcinoma of the breast, lung, or kidney, or melanoma, leukemia, and lymphoma. The differential diagnosis of a primary thyroid tumor from a metastatic tumor may become challenging in patients presenting with new thyroid nodule and a history of malignancy[57-59]. This is especially true if the neoplasm was in distant past. Immunocytochemistry can be applied in FNA cytology to help solve these dilemmas if the morphology is not characteristic[53].

For reliable diagnosis of malignancy multiple criteria should be used. Specimens could be diagnosed as 'suspicious' when cells show atypical features suggestive of but not diagnostic for malignancy. These diagnoses are useful, because they lead to surgical biopsy or excision of the lesion.

Future Trends

In spite of the profusion of work available, only marginal success has been achieved in separating indeterminate follicular lesions. Parameters used for these purpose include morphologic features, such as cellular patterns, morphometric criteria such as nuclear diameter, number and margination of nucleoli, and flow cytometry, either singly or in combination. The sensitivity of these results varied from 40%[60] to 75%[61]. No clinical or laboratory test is sensitive and specific enough to distinguish reliably

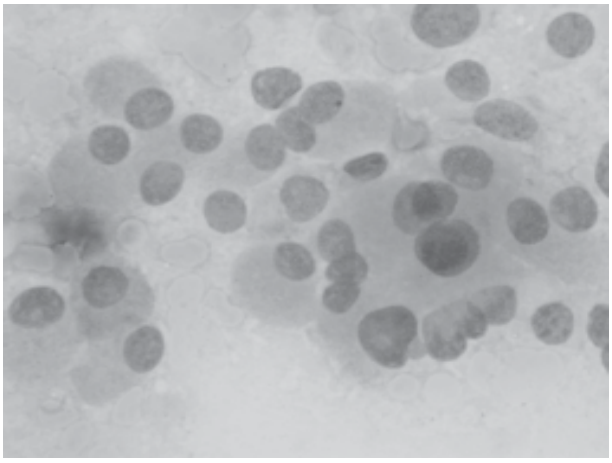

Fig. 5. *FNA of medullary carcinoma. Round to oval cells with eccentric nuclei and abundant cytoplasm with red granules (May-Grünwald-Giemsa stain, x1000).*

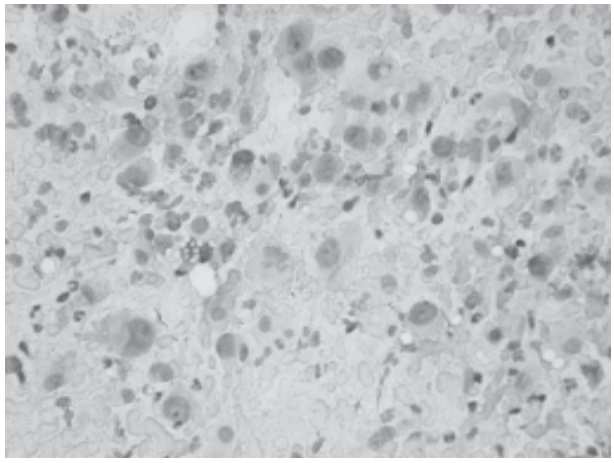

Fig. 6. *FNA of anaplastic carcinoma. Bizarre, pleomorphic cells with irregular nuclei, prominent nucleoli and mitoses (May-Grünwald-Giemsa stain, x400).*

whether a follicular neoplasm identified on FNA is benign or malignant. So, follicular lesions must be regarded as suspicious and management is controversial. Age, clinical features and discussion with patient will influence the decision on surgery, however, many centers suggest surgical excision of all indeterminate follicular lesions to make definite histologic diagnosis. This position may be changed with the development of molecular approaches to diagnosis. Several molecules have been identified immunochemically and by reverse-transcriptase PCR as potential targets for immunodiagnosis. Among these molecules, CD44v6 and galectin-3 seem to be promising markers for the detection of the presence of disregulated cell growth and of thyrocytes that have undergone neoplastic transformation[62-65]. Galectin-3 is a valuable tumor marker for thyroid malignancies of follicular epithelial cell origin. This inexpensive and simple test, which combines morphological and molecular evaluation, enhances the accuracy of differential diagnosis between benign and malignant thyroid neoplasms, improves clinical management of thyroid lesions, and could contribute to the classification of as yet undefined thyroid lesions. The wider application of this test method should help prevent unnecessary surgical procedures and use of radiolabeled iodine compounds in the diagnosis of thyroid cancers.

Although there is no agreement on the optimum diagnostic strategy for the patient with nodular thyroid disease[66], FNA thyroid cytology remains the most cost-effective, first-line diagnostic technique.

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Sažetak

ASPIRACIJSKA CITOLOGIJA ŠTITNJAČE

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Aspiracijska citologija štitnjače tankom iglom rabi se kao dijagnostička metoda već 40 godina. Glavni cilj aspiracijske citologije štitnjače je razlučiti čvorove štitnjače koji zahtijevaju kirurško liječenje od onih čvorova kod kojih to nije potrebno. Osjetljivost aspiracijske citologije štitnjače varira između 65% i 99%, a specifičnost između 72% i 100%. Preporuča se provoditi ju uz nadzor ultrazvuka, poglavito kod malih, dublje smještenih čvorova. Kod čvorova promjera manjeg od 3 cm dovoljno je izvršiti jednu do četiri aspiracije. Premda se kriteriji za prikladnost uzorka razlikuju od ustanove do ustanove, većina ih zahtijeva prisutnost folikularnih stanica. Citološka dijagnoza bolesti štitnjače zapravo je kliničko-citološka dijagnoza, jer se temelji na korelaciji citomorfološke slike i dostupnih kliničkih podataka. U našoj ustanovi dijagnostičke citološke promjene štitnjače dijelimo u tri glavne kategorije: benigne, neodređenog značaja i maligne. Benigne promjene uključuju dijagnoze kao što su benigni čvor štitnjače, nodularna struma i tireoiditis. Promjene neodređenog značaja uključuju celularnu folikularnu promjenu, folikularni tumor i tumor Hürthleovih stanica. Maligne promjene uključuju papilarni karcinom, slabo diferencirani folikularni karcinom, medularni karcinom, anaplastični karcinom, limfom velikih stanica i metastatski karcinom. Niti jedan klinički ni laboratorijski test nije dovoljno osjetljiv ni specifičan da bi pouzdano razlučio maligne od benignih citološki dijagnosticiranih folikularnih tumora štitnjače. Ovakvo stanje moglo bi se izmijeniti primjenom molekularne dijagnostike tumora pričem se CD44v6 i galektin-3 nameću kao obećavajući biljezi malignih stanica podrijetla folikularnih epitelnih stanica.

Ključne riječi: *Bolesti štitnjače, patologija; Neoplazme štitnjače, patologija; Biopsija, igla; Citodijagnostika*