

FINE NEEDLE ASPIRATION OF HÜRTHLE CELL NEOPLASMS OF THE THYROID: A CLINICOCYTOMORPHOLOGIC STUDY

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SUMMARY – Cytologic diagnosis of Hürthle cell neoplasm (HCN) includes both Hürthle cell adenoma (HCA) and Hürthle cell carcinoma (HCC). They are indistinguishable on the basis of cytologic examination because the criteria of malignancy are based on tissue architectural features of capsular and/or vascular invasion. All patients with subsequent histopathologic diagnosis of HCN of the thyroid and preoperative cytologic evaluation by fine needle aspiration (FNA) during the last six years were studied for a number of cytomorphologic features and clinical parameters (age, gender and nodule size) to determine the factors predictive of carcinoma. There were 17 cases in total, including 4 HCC and 13 HCA cases. Carcinoma was diagnosed in three of 13 (23%) women and in one of four (25%) men. Age range was 32-75 (median 57) years in adenoma patients and 46-70 (median 58) years in carcinoma patients. The mean tumor size was 4.5 ± 3.41 cm and 3.07 ± 1.82 cm in HCC and HCA patients, respectively. The cytomorphologic features indicative of HCC *versus* HCA were syncytial clusters and Hürthle cells with large nucleoli, whereas Hürthle cells showing pronounced nuclear and cellular pleomorphism in monolayered sheets with small nucleoli appeared to be characteristic of HCA ($p < 0.05$ both). The presence of Hürthle cells in syncytial clusters with large nucleoli in thyroid nodule FNA should alert the observer of the possible HCC.

Key words: *Thyroid neoplasms, pathology; Thyroid neoplasms, diagnosis; Adenoma, pathology; Carcinoma, pathology; Biopsy, needle*

Introduction

Hürthle cell neoplasm (HCN) is defined as an encapsulated group of follicular cells with at least a 75% Hürthle cell component, and includes both Hürthle cell adenoma (HCA) and Hürthle cell carcinoma (HCC). Their biologic behavior and the rationale for considering them as a distinctive clinicopathologic entity are debated¹⁻⁴. However, the frequency of malignant transformation and the biological aggressiveness of HCNs exceed those observed in other differentiated follicular tumors^{1,2}. HCA and HCC are indistinguishable from one another on the basis of cytologic examination because the criteria of malignancy are

based on tissue architectural features of capsular or vascular invasion^{1,5,6}. Aspirates are monomorphic, highly cellular with cells that show little cohesiveness and have characteristic abundant, granular cytoplasm with well-defined margins. The fine needle aspiration (FNA) diagnosis of HCN is made when there is a predominance of Hürthle cells, comprising greater than 75% of all cells, without a thyroiditis background¹. The cytologic diagnosis of HCN is an indication for surgical intervention because this diagnosis implies that a HCC has not been excluded on the basis of cytologic examination.

The purpose of this study was to determine whether specific clinical parameters and cytomorphologic features could be used in patients with HCN cytologic finding, to predict an increased probability of malignant HCN, thus identifying patients who may benefit from a more extensive surgical thyroid procedure.

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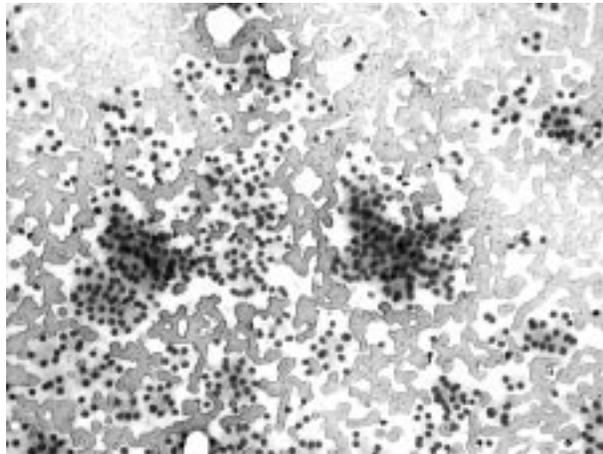


Fig. 1. FNA of a Hürthle cell neoplasm of the thyroid

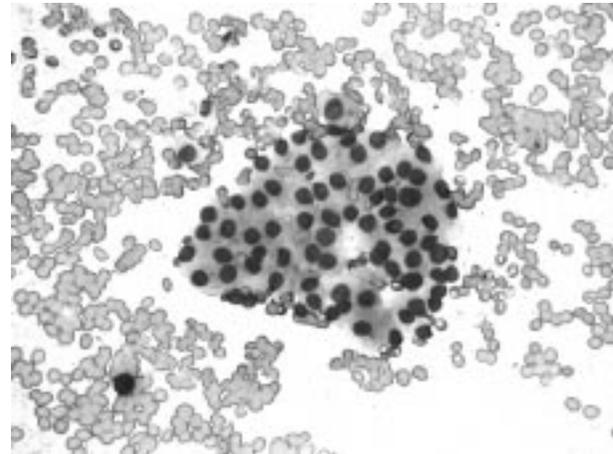


Fig. 2. FNA of a Hürthle cell neoplasm of the thyroid

Patients and Methods

All patients with preoperative cytologic evaluation by ultrasonographically guided FNA of the thyroid during the last six years, who had been surgically treated at the Department of Otorhinolaryngology & Head and Neck Surgery, Sestre milosrdnice University Hospital, and had subsequent histopathologic diagnosis of HCN, were studied for a number of cytomorphologic features and clinical parameters (age, gender and nodule size) to determine whether these factors are predictive of carcinoma.

Routine percutaneous ultrasonographically guided FNA was performed using a 23-gauge needle attached to a 10-mL syringe. The aspirated material was smeared on glass slides, air-fixed, stained by May-Grünwald-Giemsa method, and examined under a light microscope.

The following cytomorphologic features were assessed in each individual case: cellular pattern (acinar formation, monolayered sheets, papillary formations, syncytial pattern, and single-cell pattern), nuclear enlargement (none

or mild, pronounced), cellular and nuclear pleomorphism (none or mild, pronounced), nucleoli (none, small, large), cytoplasmic nuclear inclusions, cytoplasmic vacuoles, and capillary vascularization. Glass slides of one female patient with HCC (FNA finding was cellular follicular lesion) were missing, so she was not included in the cytomorphologic analysis.

Differences in gender, range and median for age, range and mean \pm standard deviation (SD) for nodule size, and presence of cytomorphologic features on FNA specimen were determined for patients with HCA (Fig. 1) and HCC (Fig. 2). Statistical analysis was performed with Fisher exact test. A *p* value less than 0.05 was considered significant. In addition, the percentage of HCCs and HCAs exhibiting each of the cytomorphologic features assessed was calculated.

Results

There were 17 cases in total, including four HCC and 13 HCA cases. The patient population consisted of 13 women and four men (male to female ratio, 1:3.25).

The incidence of malignancy was 25% (one of four) in males and 23% (three of 13) in females. Age range was 32-75 (median 57) years in adenoma patients and 46-70 (median 58) years in carcinoma patients. The mean \pm SD for nodule size was 4.5 ± 3.41 cm (range 1-9 cm) in HCC patients and 3.07 ± 1.82 cm (range 0.8-6 cm) in HCA patients (Table 1).

Among 13 patients with a histopathologic diagnosis of HCA, there were 3 aspirates classified as follicular neoplasm, 3 as HCN, 6 as suspect of HCN, and 1 aspirate was

Table 1. Clinical parameters in patients with Hürthle cell carcinoma and Hürthle cell adenoma

	PHD	
	HCC	HCA
Gender (M:F)	1:3	3:10
Age (yrs)	46-70 (median 58)	32-75 (median 57)
Nodule size (cm)	4.5 ± 3.41	3.07 ± 1.82

PHD=pathohistologic diagnosis; HCC=Hürthle cell carcinoma;
HCA=Hürthle cell adenoma

Table 2. Cytomorphologic features indicative of Hürthle cell carcinoma versus Hürthle cell adenoma

Cytomorphologic feature	HCC (%)	HCA (%)
Large nucleoli ($p < 0.05$)	100	0
Syncytial clusters	67	17

HCC=Hürthle cell carcinoma; HCA=Hürthle cell adenoma

not diagnostic. The reported FNA diagnoses for the four patients with HCC were as follows: 2 follicular neoplasms, 1 suspect for HCN, and 1 cellular follicular lesion.

Cytomorphologic features indicative of HCC versus HCA included syncytial clusters (65% vs. 17%; $p > 0.05$) and Hürthle cells with large nucleoli (100% vs. 8%; $p < 0.05$) (Table 2). Hürthle cells showing pronounced nuclear (83% vs. 33%) and cellular (92% vs. 33%) pleomorphism in monolayered sheets (75% vs. 33%; $p > 0.05$) all with small nucleoli (83% vs. 0; $p < 0.05$) appeared to be characteristic of HCA (Table 3). The following cytomorphologic features appeared to be of no value in predicting malignant HCN: cytoplasmic nuclear inclusions, cytoplasmic vacuoles, and capillary vascularization.

Discussion

The two aims of this study were to determine the role of cytomorphologic features and clinical parameters in predicting malignant HCN. Although both aims are common to any clinicopathologic study on human neoplasia, in case of HCN they assume specific significance and urgency because of the controversy surrounding this entity. In terms of behavior, some investigators believe that they are variants of follicular neoplasms (i.e. follicular adenomas and carcinomas) with very similar clinical behavior⁷⁻⁹, whereas others contend that their behavior is unpredictable and that distinction between benign and malignant HCNs is not easy to make by the conventional criteria used

Table 3. Cytomorphologic features indicative of Hürthle cell adenoma versus Hürthle cell carcinoma

Cytomorphologic feature	HCC (%)	HCA (%)
Monolayered sheets	33	75
Small nucleoli ($p < 0.05$)	0	83
Nuclear pleomorphism	33	83
Cellular pleomorphism	33	92

HCC=Hürthle cell carcinoma; HCA=Hürthle cell adenoma

for follicular neoplasms⁴. Other studies support the premise that, although HCAs behave in a benign fashion, HCCs pursue a much more aggressive course than follicular carcinomas¹⁰. Despite the varying opinions, most authors accept unequivocal capsular and/or vascular invasion as the *sine qua non* criterion for the diagnosis of malignancy^{2,7,11}.

In our series, using the histologic criteria of full-thickness capsular and/or vascular invasion, we identified 17 HCNs, of which 4 (24%) were malignant, a relatively low incidence compared with some series¹²⁻¹⁵, but similar to others^{11,16}. The female preponderance (13 patients, 76%) was similar to other series^{11,16-19}. Some of the reports indicate that there was no statistically significant relationship between age and malignancy, and our results were also in accordance with this suggestion²⁰⁻²². Some authors claim that the greater diameter of the tumor, the higher the risk of malignancy. In the study of Thompson *et al.*⁴, tumors greater than 2 cm had a high risk of malignancy. Carcangiu *et al.*¹¹ have shown that in a cohort of 153 patients none of the tumors of less than 1 cm was malignant and none of the tumors greater than 10 cm was benign. Although the number of cases was limited, our results were also in accordance with these findings.

Although FNA of the thyroid is a reliable method to identify Hürthle cell nodules likely to be neoplastic and requiring surgical excision, cytology appears to be less reliable in predicting HCC. Fine needle aspirates of HCNs have typically been described as very cellular and showing a relatively monotonous population of Hürthle cells, singly or in dyshesive aggregates associated with little or no colloid, absence of lymphocytic infiltrate, and scarcity of ordinary follicular cells. Neoplastic Hürthle cells have enlarged, generally eccentric and occasionally pleomorphic nuclei and characteristically prominent nucleoli^{23,24}.

Our findings indicated that two cytomorphologic features were more predictive of HCC against HCA: syncytial clusters (67% vs. 17%) and Hürthle cells with large nucleoli ($p < 0.05$). In contrast, Hürthle cells in fine needle aspirates of HCA occurred mostly in monolayered sheets (75% vs. 33%) with small nucleoli ($p < 0.05$) and pronounced nuclear and cellular pleomorphism.

In conclusion, although the number of cases was limited and the differentiation between benign and malignant lesions was not possible, it seems that the presence of syncytial clusters of Hürthle cells with large nucleoli in the FNA of a thyroid nodule should alert the observer of the possibility of HCC.

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Sažetak

ASPIRACIJSKA PUNKCIJA TANKOM IGLOM TUMORA HÜRTHLEOVIH STANICA:
KLINIČKO-CITOMORFOLOŠKA STUDIJA*I. Tabain, N. Mateša i Z. Kusić*

Citološka dijagnoza tumora Hürthleovih stanica uključuje i adenom i karcinom Hürthleovih stanica. Oni se ne razlikuju jedan od drugoga na osnovi citološkog pregleda, jer kriterij za malignost počiva na histološkim obilježjima invazije čahure i/ili krvnih žila. U svih bolesnika s patohistološkom dijagnozom tumora Hürthleovih stanica štitnjače i citološkom evaluacijom prije operacijskog zahvata u posljednjih šest godina analizirane su brojne citomorfološke značajke i klinički parametri (dob, spol, najveći promjer čvora) da bi se odredili čimbenici koji bi upućivali na karcinom. Ukupno je bilo 17 bolesnika: 4 s karcinomom i 13 s adenomom Hürthleovih stanica. Karcinom je dijagnosticiran u jednog (25%) od 4 muškarca i u 3 (23%) od 13 žena. Dobni raspon u bolesnika s adenomom bio je 32-75 (medijan 57) godina, a u bolesnika s karcinomom 46-70 (medijan 58) godina. Prosječna veličina čvora u bolesnika s karcinomom bila je $4,5 \pm 3,41$ cm, a u bolesnika s adenomom $3,07 \pm 1,82$ cm. Citomorfološke značajke koje su upućivale na karcinom Hürthleovih stanica bile su sincicijske nakupine Hürthleovih stanica s velikim jezgicama ($p < 0,05$). Hürthleove stanice u pločastim nakupinama s malim jezgicama ($p < 0,05$) i značajnim pleomorfizmom stanica i jezgara bile su obilježje adenoma Hürthleovih stanica. Nalaz Hürthleovih stanica s velikim jezgicama u sincicijskim nakupinama mogao bi upozoravati na karcinom Hürthleovih stanica.

Ključne riječi: *Neoplazme štitnjače, patologija; Neoplazme štitnjače, dijagnostika; Adenom, patologija; Karcinom, patologija; Biopsija, igla*