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CLINICAL INVESTIGATION

Cytological and Clinical Features of Hürthle Cell Neoplasia; Review of the Literature Due to Three Cases*

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Introduction

Hürthle cell or oncocytic thyroid neoplasms are relatively rare tumors of follicular origin (1). Hürthle cell tumors of the thyroid are defined as neoplasms composed predominantly (more than 75%) of follicular cells with oncocytic features (2,3). Hürthle cell tumors can be identified as adenoma or carcinoma. Almost all reports classify oncocytic nodules as malignant when capsular and/or vascular invasion is present or when there is perithyroid tissue infiltration or lymphatic or hematogen metastasis. A clear differentiation between adenoma and carcinoma can be determined by histopathological study (4).

Fine needle aspiration (FNA) biopsy is used successfully in the cytologic identification of Hürthle cell neoplasms as a group. However, FNA biopsy is insufficient to discriminate benign Hürthle cell from malignant Hürthle cell lesions. For this reason, in the preoperative evaluation, some clinical parameters were also suggested in the discrimination of these lesions (1). We discuss here the cytological features of Hürthle cell neoplasms as a group, the distinguishing cytological

features of benign-malign Hürthle cell lesions in FNA biopsy material and the clinical and histopathological features of these lesions.

Material

We report three cases of Hürthle cell tumor here. One case was interpreted as adenoma, while the other two cases were diagnosed as carcinoma in the postoperative pathological study. Pre-operative cytologic evaluation was performed in all patients. Clinical and pathological characteristics of the cases are showed in the Table.

Case 1

A 47 year-old woman presented with an enlarged mass on the left side of her neck for 6 months. FNA biopsy revealed plentiful colloid material, macrophages, follicle cells and some oncocytic cells. The usual cytologic characteristics of the Hürthle cell adenoma or carcinoma were not present in smears. In addition, a few oncocytic cells were observed in smears (Figure 1A). Oncocytic cells had mild hyperchromatic and large nuclei. The

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Table. Clinical, cytological and pathological features of the presented cases.

Case	Age/sex	Preoperative cytological diagnosis	First surgical treatment	Postoperative macroscopical findings	Postoperative histopathology	Second surgical treatment	Second postoperative pathology
1	47/F	Colloidal goiter with oncocytic cell changes	Subtotal thyroidectomy	One nodule (2 cm) in the right lobe one nodule (4,5 cm) in the left lobe	Hürthle cell carcinoma in both lobes	Right completion thyroidectomy	One nodule (1,5 cm) in the right lobe, Hürthle cell carcinoma
2	54/F	Colloidal goiter with oncocytic cell changes	Total thyroidectomy	One nodule (4,5 cm) in the right lobe	Hürthle cell neoplasm/adenoma	-	-
3	49/M	Hürthle cell neoplasm	Total thyroidectomy	One nodule (3,5 cm) in the right lobe, one nodule (2,5 cm) in the isthmus	Hürthle cell carcinoma in the right lobe, Hürthle cell neoplasm/adenoma in the isthmus	-	-

nucleus/cytoplasm ratio was high in these cells. FNA biopsy was interpreted as a colloidal goiter with oncocytic cell changes. Thereupon, the patient underwent subtotal thyroidectomy. Intraoperative pathology consultation was not performed during surgery. Postoperative histopathology was concordant with Hürthle cell carcinoma involving both thyroid lobes. In the subtotal thyroidectomy material, the nodule determined in the right lobe was 2 cm in longest diameter, while the nodule in the left lobe was 4,5 cm in diameter. Completion thyroidectomy was then done. The completion thyroidectomy specimen also had Hürthle cell carcinoma in the right thyroid lobe. The second tumoral nodule in the right lobe was 1,5 cm in diameter. The tumor did not infiltrate outside the thyroid capsule. The performed limited neck dissection material had five reactive lymph nodes.

Case 2

A 54 year old woman had subclinical hyperthyroidism for 2 years. The physical examination and ultrasonography (US) showed multiple nodules in the left

lobe and one nodule in the right lobe. Systemic examination was unremarkable. FNA biopsy revealed cells showing oncocytic changes and scant colloid. A few oncocytic cells showed hyperchromatic nuclei and high nucleus/cytoplasm ratio. However, in the smears, oncocytic cells were very few. Therefore, on the basis of present cytologic findings, the case was diagnosed a colloidal goiter with oncocytic cell changes. The patient underwent total thyroidectomy. During the surgery, intraoperative pathology consultation was not made. Macroscopical examination showed a nodular lesion with capsule, 4,5 cm in longest diameter in the right lobe. The histopathological analysis of this nodule revealed a Hürthle cell neoplasm. No capsular or vascular invasion was observed. Therefore, for this lesion, it was agreed that it would more likely be a Hürthle cell adenoma.

Case 3

A 49 year old man presented with a mass on the left side of his neck. US showed two nodules in the right lobe and isthmus. FNA biopsy exhibited some oncocytic cells of syncytial character (Figure 1B) and large oncocytic cells

with pyknotic nuclei and abundant eosinophilic granular cytoplasm (Figure 1C). Additionally, scant colloid material and some denuded thyroid follicle cell nuclei were present. FNA cytology was interpreted as a Hürthle cell neoplasm. The patient underwent total thyroidectomy. Intraoperative pathology consultation was not performed during the surgical operation. In the postoperative macroscopical examination, the longest diameter of nodule in the right lobe was 3,5 cm (Figure 1D). The nodule localized in the isthmus was 2,5 cm in its greatest dimension. In postoperative pathology, Hürthle cell neoplasms were determined, as two separate foci both the right lobe and the isthmus. The nodular tumoral lesion determined in the right lobe was interpreted as Hürthle cell carcinoma due to clear capsular and vascular invasion (Figure 1E). Many Hürthle cells showed evident pleomorphic, hyperchromatic nuclear figures (Figure 1F). The nodule in the isthmus was concordant with Hürthle cell adenoma. Capsular and vascular invasion were not observed.

Discussion

The incidence of Hürthle cell neoplasms ranges widely from 0,4% to 10% of all thyroid tumors in large series (4-10). The affected patients are more frequently females in 5th to 7th decades. Male/female ratio is reported between 1/3-1/5 in different series (6,8,11-15). Male patients exhibit a lower incidence of Hürthle cell neoplasm on the whole. However, Hürthle cell carcinomas are encountered more frequently in men (Male/female: 1,8-3/1) (9,11-13). Hürthle cell carcinomas have a more aggressive biological behavior than non-Hürthle cell follicular neoplasms. In the larger series it was found that patients with Hürthle cell carcinoma are more prone to metastasis, multifocality, and intrathyroidal and extrathyroidal invasion as compared with non-Hürthle follicular carcinoma (1). Hürthle cell neoplasms can be diversified in as adenoma and carcinoma. The histologic criteria used to distinguish benign from malignant forms are similar to criteria used for the discrimination of follicular adenoma and carcinoma and criteria for malignancy include vascular invasion, transcapsular penetration and destructive capsular invasion (1-4,16). The discrimination between Hürthle cell carcinoma and Hürthle cell adenoma can be only made by surgical excision and histopathological examination. FNA biopsy shows similar cytological

features for both Hürthle cell adenoma and Hürthle cell carcinoma. Unfortunately, intraoperative pathology consultation is not helpful in differentiating between these neoplasms. Therefore, lobectomy is usually performed after the FNA biopsy diagnosis of Hürthle cell neoplasm and then completion thyroidectomy is done if Hürthle cell carcinoma is diagnosed in the postoperative histopathological examination (1). Intraoperative pathology consultation was not made during the surgery in any of our cases.

In the recent literature, on the basis of cytological features of Hürthle cell neoplasms, some studies are noted to determine the distinguishing criteria of benign Hürthle cell lesions from Hürthle cell carcinomas (17-19). However, many authors suggest that the nuclear features of these neoplasms are not reliable indicators for the malignancy. Benign oncocytic nodules formed by oncocytic cells can also appear in lymphocytic thyroiditis, Graves' disease, ancient nodular goiter and furthermore oncocytic cells appeared above diseases can also show marked nuclear pleomorphism (1). Renshaw made an attempt to define criteria that are more specific for Hürthle cell carcinoma. In Renshaw's study, Hürthle cell carcinomas were tentatively identified using five criteria. These criteria; 1-Predominantly Hürthle cells, 2-Scant colloid, 3-At least one of either small cell dysplasia (cytoplasmic diameter less than twice the nuclear diameter, with often quite bland cells), 4-Large cell dysplasia (greater than twice the variation in nuclear diameter; large cells typically demonstrate prominent nucleoli and irregular nuclear outlines), 5-Crowding (nuclei touching), and dyscohesion (single cells). According to this study by focusing on criteria for Hürthle cell carcinoma rather than all Hürthle cell neoplasms, the specificity of diagnosing HCC Hürthle cell carcinoma may improve. However, 63% of Hürthle cell adenomas and 25% of the cases of nonneoplastic Hürthle cell lesions could not be classified reliably as benign (20). Besides, in the cytological examination of Hürthle cell neoplasms, Giorgadze also recommended combining cytological assessment with various clinical variables (age, size of nodule and sex) to stratify patients with a diagnosis of Hürthle cell neoplasm into a high and low risk of malignancy groups (1). In another report, Kini identified four cytological characteristics of Hürthle cell carcinomas: 1-Syncytial tumor tissue fragments; 2-Small tumor cells with a high nuclear/cytoplasmic ratio; 3-Prominent,

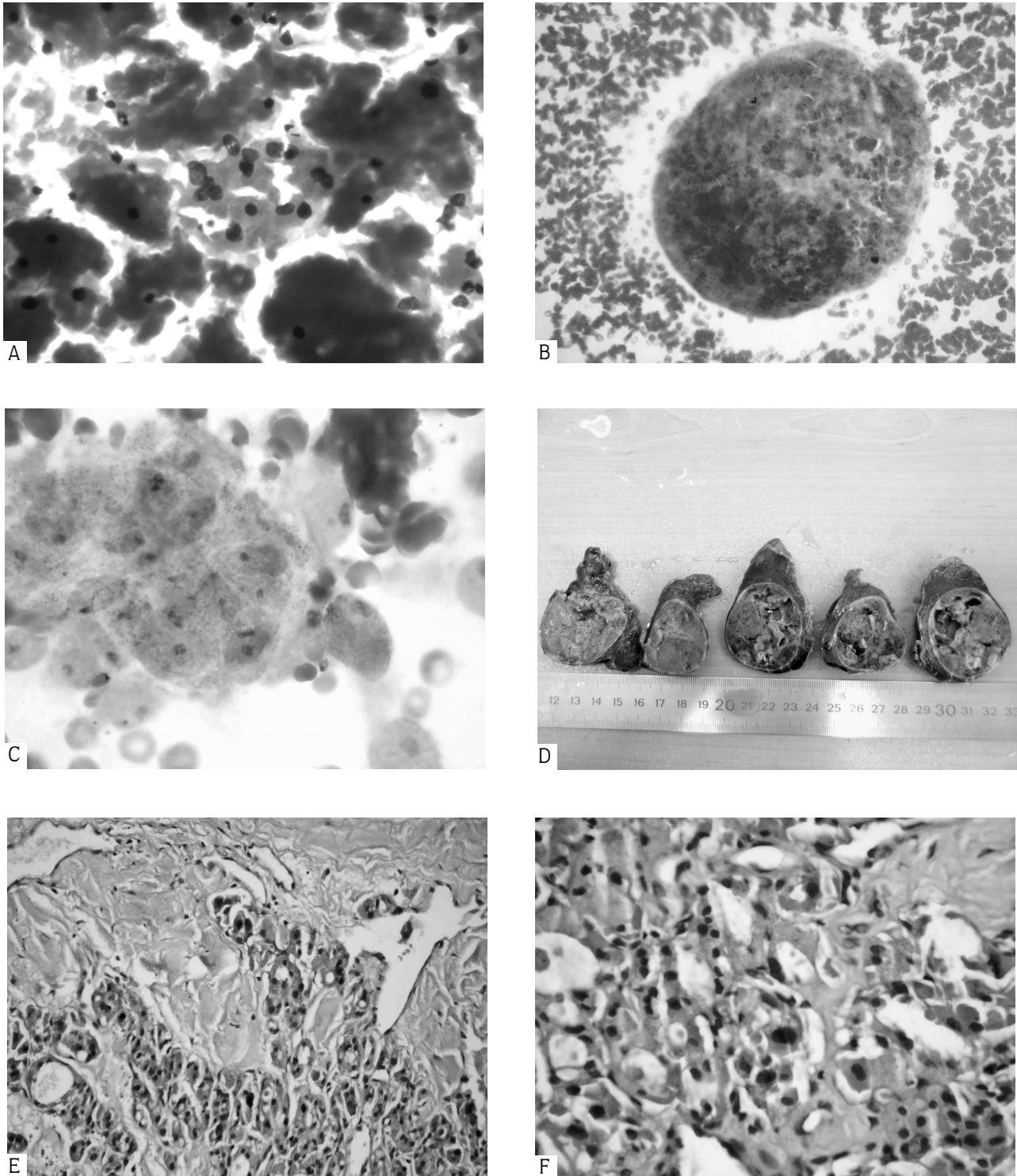


Figure 1 (A): Oncocytic cells on FNA biopsy (MGG, x25). (B): Oncocytic cells in syncytial character on FNA biopsy (MGG, x15). (C): Oncocytic cells with abundant granular cytoplasm on FNA biopsy (MGG, x40). (D): Macroscopical appearance of cystic, degenerated tumoral lesion with capsule in Hürthle cell carcinoma. (E): Vascular invasion of atypical Hürthle cells on histological section (HE, x15). (F): Atypical Hürthle cells with pleomorphic, hyperchromatic nuclei on high power magnification (HE, x30).

regular or irregular nucleoli and 4-Intranuclear cytoplasmic inclusions (3,21). Using these criteria, Kini was able to identify about 60% of Hürthle cell carcinoma by FNA.

A preoperative cytological study was performed in all our case, but, none of our patients could be given a definitive diagnosis in the preoperative period. In two cases (case 1 and case 2) FNA biopsy smears were interpreted as colloidal goiter with oncocytic cell changes. In both cases FNA biopsy smears were not optimum for cellularity. Their postoperative histopathologies were concordant with Hürthle cell carcinoma and Hürthle cell neoplasm/adenoma, respectively. The cytology slides of all cases were reviewed. FNA biopsy smears of case 1 showed a few oncocytic cells with hyperchromatic nuclei, high nuclei/cytoplasm ratio, granular cytoplasm among the intense erythrocytes piles. Appearance of these cells fitted with large cell dysplasia, but these cells were rarely observed. In addition, scant colloid material, macrophages and follicle cells were present in the slides. In the slides of case 2, some oncocytic cells with hyper or normochromatic nuclei, and higher nuclear/cytoplasm ratio were noted. Scant colloid and macrophages were observed in smears of FNA biopsy as in those of case 1. Both cases' cytological findings were similar. Because oncocytic cells were too few in smears, we could not interpret a definitive diagnosis other than colloidal goiter with oncocytic cell features. However one (case 1) of these cases was reported as Hürthle cell carcinoma, while the other (case 2) was diagnosed as Hürthle cell neoplasm/adenoma on postoperative histopathological examination. Preoperative cytology unfortunately failed in the discrimination of these lesions. In case 3, FNA biopsy findings were more definitive than those of the other two cases. This case was interpreted as Hürthle cell neoplasm on preoperative cytology. When the slides were reevaluated, more oncocytic cells than those of other two cases were observed. Oncocytic cells had rather large granular cytoplasm and pyknotic nuclei and were totally uniform in appearance. Postoperative histopathology of this case was reported as Hürthle cell carcinoma. Nuclear atypia and pleomorphism were not present in smears. However, as all cells were oncocytic in character, preoperative cytological examination was interpreted as Hürthle cell neoplasm.

In Giorgadze's study, clinical characteristics associated with malignancy such as older age (older than 40 years),

size of the nodule (lesions measuring more than 2 cm) and sex (malignant lesions were more common in male patients than female patients) were suggested (1). Malignancy in Hürthle cell neoplasms is more common in older patients. Tyler et al showed that patients older than 50 years of age with a diagnosis of Hürthle cell neoplasm had a high risk of malignancy (22). In Giorgadze's study, it was found that patients older than 40 years had a higher risk of malignancy than those younger (1). Our cases' ages ranged from 47 to 54 years. All our cases were older than 40 years. Two cases were female while one case was male. Two cases (47 and 49 year old female and male patients, respectively) had Hürthle cell carcinoma. The other female patient aged 54 years had Hürthle cell neoplasm (Table).

Bronner et al. showed that 67-80% of oncocytic/Hürthle cell neoplasms, which measured >3,5-4 cm, were histologically cancer (23). Giorgadze et al. found measuring >2 cm to be an increased risk of malignancy (1). In our cases the dimension of tumoral nodules ranged from 1,5 cm to 4,5 cm. A total of six nodular lesions of Hürthle cell neoplasm were present in our three patients. A female patient aged 47 years had separate Hürthle cell neoplasms in both thyroid lobes. One of these was 4,5 cm, while the other was 2 cm in the longest dimension and both lesions were diagnosed as carcinoma due to definite capsular and vascular invasion. Recent tumoral nodule determined in completion thyroidectomy was also concordant with Hürthle cell carcinoma, histopathologically, and the longest diameter of this lesion was measured as 1,5 cm. Tumoral nodule with 4,5 cm measuring in the longest diameter in the right thyroid lobe of the other female patient aged 54 years was diagnosed as Hürthle cell neoplasm/adenoma. This lesion did not show capsule and/or vascular invasion. The presented male patient aged 49 years had also two separate lesion and the nodular lesion in the right lobe was 3,5 cm in the longest dimension. This lesion showed clear histological features of Hürthle cell carcinoma, while the other nodular lesion with 2,5 cm in longest diameter determined in the isthmus was concordant with Hürthle cell neoplasm/adenoma. When we evaluated these tumoral lesions according to the dimension and age, we observed that two nodules with the longest and the shortest diameter (4,5 cm and 1,5 cm) were diagnosed as Hürthle cell carcinoma. The other lesion with the longest diameter (4,5 cm) was interpreted as Hürthle cell neoplasm/adenoma, which was the tumor observed in the

oldest one in our patients presented. The other two patients were diagnosed as Hürthle cell carcinoma and were relatively younger patients than the 54 years old female patient with Hürthle cell adenoma.

Hürthle cell carcinoma is considered by many as a distinct clinicopathological entity due to its clinically aggressive behavior compared with papillary and follicular carcinoma. Taking into account this aggressive nature, Thompson and Gundry suggested that all Hürthle cell neoplasms, irrespective of their size, should be regarded as malignant and treated with an aggressive surgical approach such as total thyroidectomy (1). Different ideas about the biological behavior of Hürthle cell neoplasms may also be conflicting. In general, it is currently believed that a Hürthle cell neoplasm should be considered as clinically benign due to the relevant percentages of extended survival. However, there have been several observations of recurrence and/or distant metastases even after very long follow-up (4). Some large series studies showed that none or only a few of cases diagnosed as Hürthle cell adenoma or neoplasm presented with local recurrences, lymph node or distant metastases after an average follow up of 8 to 9 years (11,13,15).

In the matter of Hürthle cell carcinoma, some authors consider them as a variant of follicular carcinoma. However, others suggest that Hürthle cell carcinomas had a more negative prognosis (5,9,11). Although both opinions are supported by different series of prognostic studies, the studies show that the average survival rates in the cases of Hürthle cell carcinoma are lower than those of follicular carcinomas (7,11,24-29).

These confusing observations have caused the development of different therapeutic regimes. Some that relied on the usually benign behavior of Hürthle cell neoplasms support limited thyroid resection. These authors believe that no long term recurrence may occur even in cases bearing Hürthle cell carcinoma and therefore, they suggest simple lobectomy (30). Authors who believe that Hürthle cell neoplasms are all potentially malignant suggest that total thyroidectomy should be performed in cases of carcinoma and adenoma with suspicious histological features (5,6-9,11,13,15,31). Thompson and Azadian consider that all Hürthle cell neoplasms must be treated by total thyroidectomy because of the inadequate available criteria of differentiation between Hürthle cell adenomas and carcinomas (12,32).

According to generally accepted opinion, follow up in Hürthle cell carcinomas should be closer and more extended than for other thyroid tumors, as local recurrences or metastases may become evident more than 15 years after the diagnosis and initial treatment. A large case study revealed 35,7% recurrence in residual thyroid parenchyma and/or soft neck tissues (75% after enucleation, 40% after lobectomy and 15% after total thyroidectomy) (11). Lymph node involvement, mainly the laterocervical ones, is seen in 5-30% of the Hürthle cell carcinoma cases (7,8,9,31,33). Distant, hematogenous metastases involve mainly lung, brain, liver and bones (5,6,9,34). Distant metastases are observed in 34% of Hürthle cell carcinoma cases. The distant metastases as a part of first clinical presentation are noted in 10-20% of the cases (2).

In conclusion, Hürthle cell neoplasms are tumors with potentially malignant behavior. More conservative therapeutic approach is offered for Hürthle cell adenomas. However, in preoperative cytological examination, unfortunately, clear differentiating criteria are not present between Hürthle cell adenoma and carcinoma, therefore, definite discrimination between malignant and benign Hürthle cell lesions can be made only in the postoperative histopathological examination. Some researches have attempted to improve preoperative cytological diagnosis. For this objective, these authors have suggested that certain cytological criteria should be evaluated as a group. This approach improved the preoperative diagnosis to some degree. In addition, it is stated that some clinical parameters (age, dimension of the nodule and sex) should be added to the cytological evaluation for more definite preoperative cytological diagnosis. We consider that oncocytic cells in FNA biopsy smears should be an alert, regardless of oncocytic cell number and the degree of pleomorphism or atypia in the oncocytic cells. In this condition, intraoperative pathology consultation, despite limited diagnostic value of frozen section, should be proposed during the surgery.

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