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Hurthle Cell Neoplasm of the Thyroid: Still a Dilemma?

Tiroidin Hurthle Hücreli Neoplazisi: Hala İkilem mi?

Dilek Tüzün, Ayten Oğuz, Murat Şahin, Kamile Gül

Sütçü İmam University Faculty of Medicine, Department of Endocrinology and Metabolism, Kahramanmaraş, Turkey

Abstract

Hurthle cells are large epithelial cells producing thyroglobulin and are observed in both nonneoplastic and neoplastic thyroid lesions. Hurthle cell neoplasms are classified as benign Hurthle cell adenoma or malignant hurthle cell carcinomas. These two entities are distinguished according to the presence of thyroid capsular or vascular invasion or metastatic disease. Their biologic behavior is unpredictable. Cytomorphologic features that are associated with neoplastic disease are absence of colloid, absence of chronic inflammation, nonmacrofollicular architecture, presence of transgressing blood vessels, extensive overall cellularity, extensive Hurthle cellularity, small cell dysplasia, large cell dysplasia, crowding, and dyshesion. These cytomorphologic features that support malignancy in nodules including Hurthle cells could guide the clinicians about the approach to the patients.

Keywords: Hurthle, neoplasia, cytomorphology

Öz

Hurthle hücreleri tiroglobulin üreten büyük epitelyal hücreler olup hem nonneoplastik hem de neoplastik tiroid lezyonlarında izlenirler. Hurthle hücreli neoplaziler, benign Hurthle hücreli adenom veya malign Hurthle hücreli kanserler olarak sınıflandırılırlar. Bu iki antite tiroid kapsül veya vasküler invazyonun veya metastatik hastalık varlığına göre ayırt edilmektedir. Tümör biyolojik davranışı öngörülememektedir. Neoplastik hastalık ile alakalı sitomorfolojik özellikler; kolloid yokluğu, kronik enflamasyon yokluğu, nonmakrofolliküler yapı, kan damarı hasarı varlığı, artmış sellülarite, artmış Hurthle hücreleri, küçük hücre displazisi, büyük hücre displazisi, kalabalıklaşma ve dizhezyondur. Maligniteyi destekleyen bu sitomorfolojik özellikler Hurthle hücresi içeren nodüllere yaklaşım konusunda klinisyene kılavuz olacaktır.

Anahtar kelimeler: Hurthle, neoplazi, sitomorfoloji

Introduction

The Hurthle cell is a large, polygonal cell characterized by eosinophilic granular cytoplasm and a large, hyperchromatic nucleus with a prominent nucleolus (1). Hurthle cells are seen in many nonneoplastic conditions of the thyroid and are not specific for any disease (2,3).

Thyroid nodules containing hurthle cells in cytologic evaluation are composed of many histopathologic entities, including Hashimoto's thyroiditis (HT), Hurthle cell adenomas (HCA), Hurthle cell carcinomas (HCC), variants of papillary thyroid carcinoma, including tall cell variant, oncocytic variant, and warthin-like variant, and the oncocytic variant of medullary carcinoma (4,5).

Hurthle cell neoplasms (HCNs) are rare tumors. They have an unpredictable biology. There are difficulties in distinguishing Hurthle cell adenoma from carcinomas in preoperative and intraoperative period. Few institutions have extensive experience in following up patients with Hurthle cell predominant thyroid nodules. The aim of this review was to examine the features of Hurthle cell neoplasia which would be important in the treatment of patients and could guide clinicians.

Hurthle Cell

Hurthle cells are large epithelial cells that produce thyroglobulin and are observed in both nonneoplastic and neoplastic thyroid lesions (6). These cells, which were originally described by Hurthle in 1894, are now considered to be derived from parafollicular cells or C cells. The oncocytic cells which are now defined as Hurthle cells (derived from follicular cells were actually described by Askanazy in 1898 (1). But in the literature, to describe follicular-derived epithelial cells with oncocytic cytology, the term Hurthle cells is still used. The term Hurthle cells also includes eosinophilic, oncocytic, and oxyphilic cells (2). Cytologically, Hurthle cells are large polygonal cells with eosinophilic abundant granular cytoplasm, large hyperchromatic nuclei and prominent nucleoli (Figure 1). The cell borders seperated sharply and windows can be seen between adjacent Hurthle cells. In addition, in papanicolaou-stained smears, intranuclear grooves can be seen in Hurthle cells (2,7). Hurthle cell cytoplasm contains thousands of mitochondria shown by using electron microscopy. The mitochondria often contain dense core granules and filamentous inclusions. Secondary to defects in mitochondrial deoxyribonucleic

Address for Correspondence: Dilek Tüzün MD, Sütçü İmam University Faculty of Medicine, Department of Endocrinology and Metabolism, Kahramanmaraş, Turkey
Phone: +90 344 288 37 68 E-mail: tuzund@gmail.com **Received:** 09/06/2015 **Accepted:** 22/10/2015

acid (DNA), numerous mitochondria may be seen in Hurthle cells. If a decrease in mitochondrial activity occurs secondary to DNA changes, an increase in the number of mitochondria may follow. In HCNs, point mutations in the mitochondrial genes also has been reported (1).

Hurthle cells are seen in many nonneoplastic conditions of the thyroid, such as autoimmune thyroiditis, multinodular goiter, Hurthle cell metaplasia, and in the thyroids of patients who have been treated with head and neck irradiation and systemic chemotherapy (1,2,3,8,9). Diffuse or focal Hurthle cell changes can be seen in the thyroids of patients who have hyperthyroidism for a long time. In many of these nonneoplastic conditions, Hurthle cells are found as isolated cells but in some cases, numerous oncocytes can be found in the nodules (1). Chronic lymphocytic thyroiditis is the classic thyroid disorder in which Hurthle cells are mostly seen. Chronic stimulation is required in alteration of chronic and follicular epithelium to Hurthle cell histology (10).

According to the classification of the World Health Organization (WHO), many phenotypes of oncocytic thyroid neoplasms can be seen. However, lesions wih follicular and solid patterns cause discussion in the diagnosis (11). Watery colloid, macrophages, intranuclear grooves, focal nuclear chromatin clearing and small follicular cells with little cytoplasm and small round nuclei with dense chromatin and prominent nucleoli are seen in nonneoplastic Hurthle cell lesions.

Hurthle cells in Hashimoto's thyroiditis can mimic papillary cancer, showing intranuclear grooves, intranuclear inclusions, and nuclear chromatin clearing. Some immunohistochemical stains, such as cytokeratin 19, galectin-3, and hector battifora mesothelial-1 can be used to solve this dilemma. However, Hurthle cells in HT can sometimes show positive immunostaining with these markers (1,12).

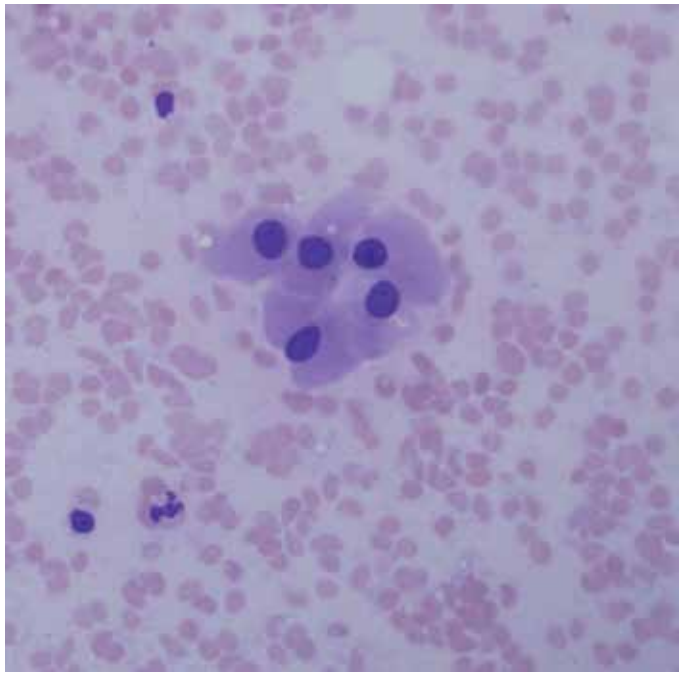

Figure 1. Hurthle cells (Hematoxylin-eosin, x40)

According to the 2004 classification of the WHO, oncocytic lesions were included as sub-groups of follicular adenoma, follicular thyroid carcinoma, papillary carcinoma, and medullary carcinoma (11,13).

There are thyroid neoplasia types characterized by oncocytic cytology (1). These are, benign neoplasia (HCA, granuler cell tumor), malign neoplasia (HCC) and papillary thyroid carcinoma variants (tall cell variant, oncocytic variant, warthin like variant), follicular carcinoma oncocytic variant and medullary carcinoma oncocytic variant.

Hurthle Cell Neoplasms

HCNs are composed of at least 75% Hurthle cells (1). They are classified as benign HCA or malignant HCC and distinguished according to the presence of thyroid vascular or capsular invasion or metastatic disease (11). HCNs have partial encapsulation and usually, they are solitary tumors. Necrosis and hemorrhage may be seen grossly, especially in lesions that have undergone preoperative fine needle aspiration biopsy (FNAB) (14,15,16). Growth patterns which are seen in HCNs are follicular, macrofollicular, solid, trabecular, and pseudopapillar, howewer, follicular growth pattern is mostly seen. Dystrophic calcifications may be seen in HCNs. They may be even in psammomatous nature within colloid and are often not lamellated (17,18). The main criteria for malignancy in HCN is the presence of capsular and/or vascular invasion, not nuclear atypia, cellular pleomorphism, mitosis (19).

Cytomorphologic features that are associated with neoplastic disease are absence of colloid, absence of chronic inflammation, nonmacrofollicular architecture, presence of transgressing blood vessels (TBV), extensive overall cellularity, extensive Hurthle cellularity, small cell dysplasia (cytoplasmic diameter less than twice the nuclear diameter, with often quite bland cells), large cell dysplasia (greater than twice the variation in nuclear diameter, crowding (nuclei touching), and dyshesion (single cells) (2,3,20,21,22). TBV were defined as capillaries passing through clusters of Hurthle cells (23). In a recent study, nuclear groove, TBV, and absence of colloid were observed with a higher frequency in malignant nodules compared to benign nodules (Figure 2, 3, 4). In cytomorphological evaluation, these are the features that seem to support malignancy in nodules including Hurthle cells cytologically (24).

In a recent study, HCNs were analysed by inter-phase fluorescence in situ hybridization and chromosomes 5, 7, 11, 12, 17, and 22 were evaluated. They showed that chromosome imbalances were common in both benign and malignant HCNs. Howewer, chromosome losses, especially chromosome 22, were more in HCC than adenomas (25).

Hurthle Cell Adenoma

These adenomas are oncocytic-type follicular adenomas. More than 75% of the specimen is composed with Hurthle cells (3). According to some authors, differentiation of HCA from HCC can be made on the basis of nuclear atypia nuclear pleomorphism, prominent nucleoli, and high nuclear-cytoplasmic ratio, but the demonstration

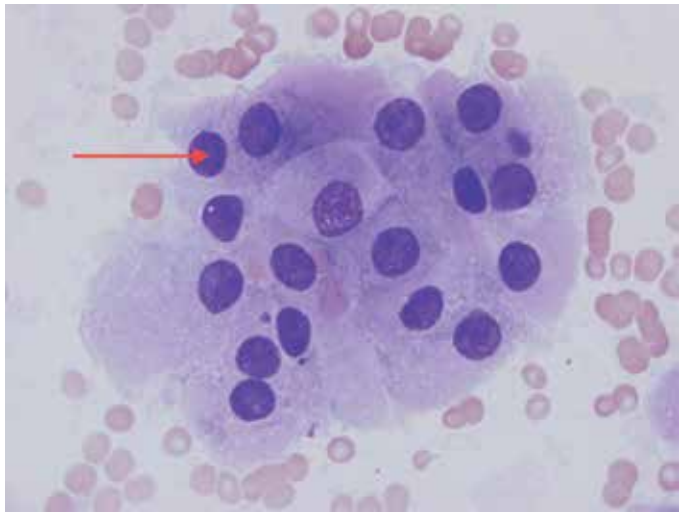

Figure 2. Nuclear groove (May Grunwald Giemsa, x40)

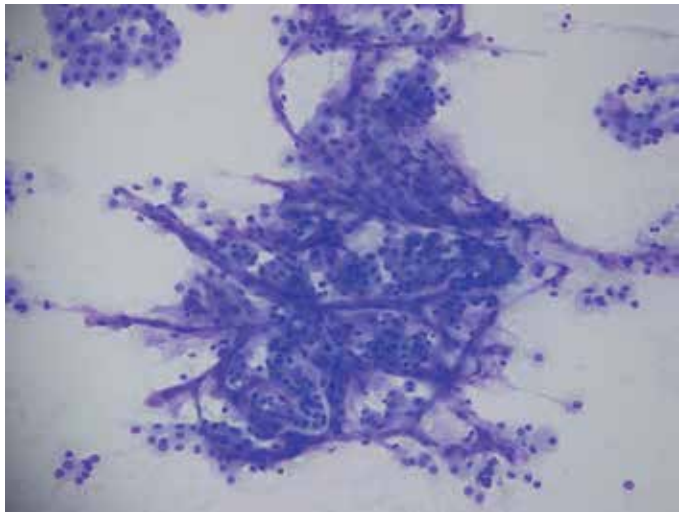

Figure 3. Transgressing blood vessels (May Grunwald Giemsa, x20)

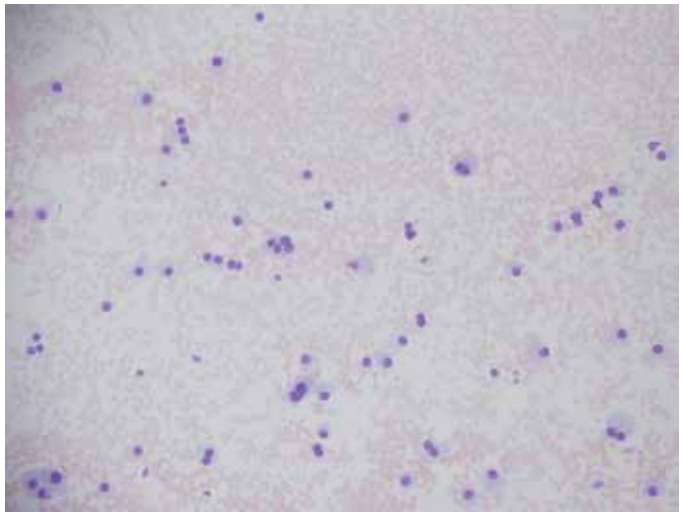

Figure 4. Absence of colloid (May grunwald giemsa, x10)

of capsular and/or vascular invasion in histopathologic examination is necessary to differentiate HCA from HCC, and FNAB cytology can not show this (1). The growth pattern of oncocytic adenomas is usually follicular, but it also can be trabecular or solid and in the background chronic lymphocytic thyroiditis is found. Oncocytic adenomas may show focal or diffuse papillary structures and dystrophic calcifications, even if in psammomatous nature within colloid and are often not lamellated (Figure 5) (13).

Hurthle Cell Carcinoma

Hurthle cell carcinoma comprise approximately 5% of differentiated thyroid carcinomas (26). HCC can be classified as minimally invasive, invasive, or angioinvasive follicular carcinomas. Hurthle cell carcinomas behave more aggressively than follicular carcinomas (1). Survival rates change between 50-60% for five years (27). Invasion of the capsule but no angioinvasion is seen in mimimally invasive tumors (Figure 6). Minimal capsular invasion and also vascular invasion are seen in angioinvasive tumors (19). Hematogenous metastases to liver, lung and bone and metastases to regional lymph nodes are reported (1). HCC is more agressive tumor than follicular carcinoma, shows a greater tendency to metastasize to distant sites and a higher mortality rate (28,29,30). Total thyroidectomy is the first choice for the treatment of HCC. Even if Hurthle cells show low uptake of iodine, after surgery, patients are often treated with iodine 131 therapy (1).

Conclusion

Thyroid nodules containing Hurthle cells are composed of a wide range of pathologic entities. Cytologic evaluation in such cases is difficult because of predominance of Hurthle cells seen in thyroid FNAB specimens of all of these entities. Immunohistochemical markers and molecular techniques have proven to be ineffective for distinguishing HCN from benign Hurthle cell lesions. But cytomorphologic features that support malignancy in nodules including Hurthle cells may be important in treatment of patients and could guide the clinicians.

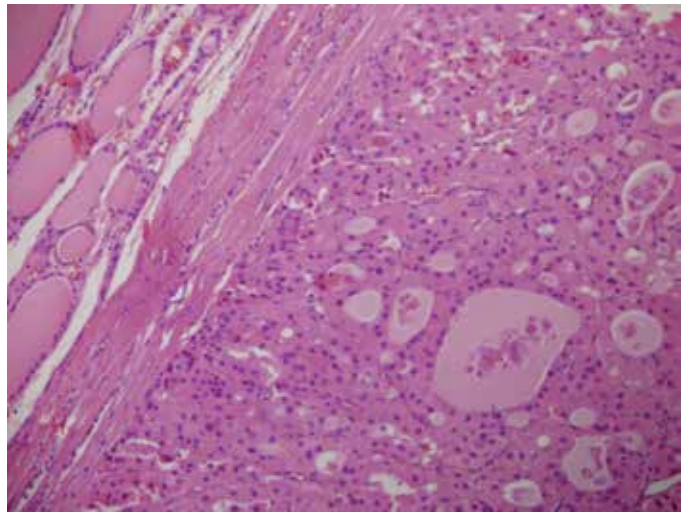

Figure 5. Hurthle cell adenoma (Hematoxylin-eosin, x40)

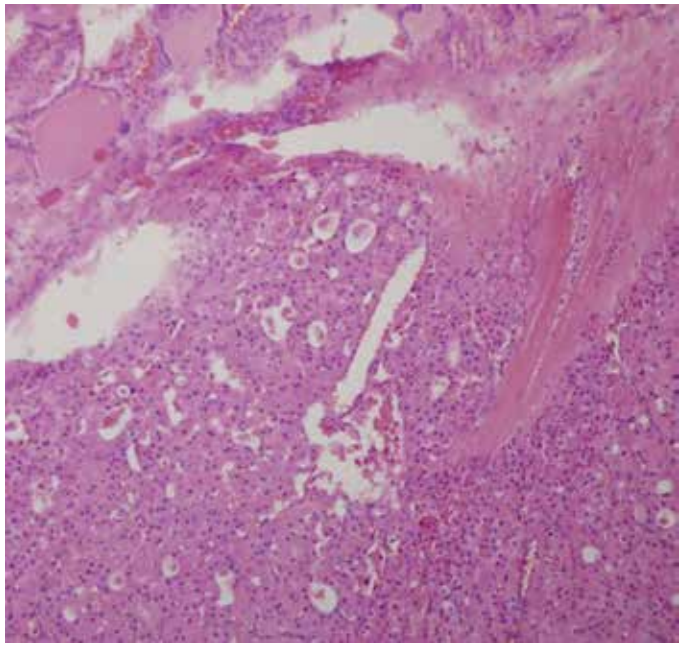

Figure 6. Hurthle cell carsinoma, capsular invasion (Hematoxylin-eosin, x40)

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Dilek Tüzün, Design: Dilek Tüzün, Ayten Oğuz, Data Collection or Processing: Dilek Tüzün, Ayten Oğuz, Murat Şahin, Kamile Gül, Analysis or Interpretation: Dilek Tüzün, Ayten Oğuz, Murat Şahin, Kamile Gül, Literature Search: Dilek Tüzün, Ayten Oğuz, Murat Şahin, Kamile Gül, Writing: Dilek Tüzün.

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