

Hurthle cell in thyroid diseases

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Abstract

The Hurthle cells originally described in 1894 by Karl Hurthle, are considered to represent ultimobranchial body-derived parafollicular cells. The oncocytic cells that we now consider to be the follicular-derived Hurthle cells were actually described by Askanazy in 1898. They are large, polygonal cells with marked eosinophilic, granular cytoplasm reflective of overly abundant mitochondria. These cells commonly occur in nodular goiters and dominant adenomatous or hyperplastic nodules.

The differential diagnosis of Hurthle cell lesions is quite broad. There are significant controversies with regard to optimal management of patients with Hurthle cell carcinoma. This review provides an overview of studies to distinguish benign from malignant Hurthle cell lesions.

Introduction

In 1894, Karl Hurthle described an intrafollicular cell of the thyroid gland found in normal canines, while acknowledging that Baber had previously described this same cell in other laboratory animals.

What Hurthle described, however, were the parafollicular C cells, not those now associated with his name. The cell now known as the HC was actually described in 1898 by Max Askanazy in patients with Graves' disease [1].

Hurthle cells (HCs) and its changes (oncocytes/oncocytic or "oxyphils/oxyphilic change) are often described on fine-needle aspiration biopsy (FNAB) of thyroid lesions. They are large, polygonal cells with marked eosinophilic, granular cytoplasm with abundant mitochondria (up to 5,000 mitochondria). The accumulation of mitochondria has been reported to be a result of alterations in the mitochondrial DNA encoding for mitochondrial enzymes, leading to proliferation through stimulation of transcription factors encoded by the nucleus [2,3].

Hurthle cells can be observed in benign and malignant conditions of the thyroid gland. The mechanism behind mitochondrial abundance in these conditions is not completely understood; however, it is likely a reflection of excessive mitochondrial proliferation and/or mitophagy.

It was believed that the Hurthle cell is a result of senescent change because they are more commonly seen in older individuals. They show limited thyroglobulin production and contain high levels of oxidative enzymes [4-7].

Hurthle cells in Thyroid Pathology

Hurthle cells may be present in nonneoplastic lesions (multinodular goiter, nodular hyperplasia, lymphocytic thyroiditis, and Graves disease) in patients who have received radiotherapy or chemotherapy, and in all types of benign or malignant neoplasms (including follicular adenoma, follicular carcinoma, follicular variant of papillary thyroid carcinoma and Hurthle cell carcinoma) [8].

The histologic distinction between adenoma and carcinoma can generally only be definitively made on histologic examination

of a resection specimen; like other follicular lesions, it is determined by the presence or absence of capsular and/or vascular invasion, or metastasis to lymph nodes or distant organs and also hypoechogenicity, microcalcifications, internal vascularity, and nodules that are taller than wide, which are the hallmarks of HC carcinoma (HCC). Hemorrhage and necrosis also may be seen in lesions that have undergone preoperative fine-needle aspiration biopsy; massive infarction either spontaneously or following fine-needle aspiration biopsy has been reported in Hurthle cell tumors [9-11].

HCC was first described by Ewing in 1928 [12]; the incidence varies between 3 and 10 % in all thyroid nodules [13].

Hurthle cell cancer has the highest incidence of metastasis among the differentiated thyroid cancers. Metastasis usually occurs hematogenously, but lymph node metastasis is also not uncommon and typically involves the regional lymph nodes [14]. Recurrent Hurthle cell carcinomas are considered to be incurable. Mortality rates vary in different series, based on the staging systems used, which consider the patient's age, tumor size, extrathyroidal tumor spread, pathologic classification of the neoplasm (Hurthle cell carcinoma versus adenoma), and the therapeutic approach. All races appear to be affected equally. The mean age is usually 50-60 years, approximately 10 years older than the age associated with other types of differentiated thyroid cancers [15].

Tumor size is an important feature for biological behavior. A study found that a Hurthle tumor that is 4 cm or larger has an 80% chance of histologic evidence of malignancy [16], and in another study of 23 patients, the mean tumor size was significantly greater for carcinomas than adenomas [17].

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Hurthle cells in Thyroid cytology

The ability to distinguish benign from malignant HC lesions of the thyroid preoperatively is very important for the management of the nodules. Cytological atypia may include necrosis, nuclear pleomorphism/crowding, greater necrosis, nuclear pleomorphism/crowding.

According to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) FNA diagnosis of a Hürthle cell neoplasm (HCN) can typically be classified as a follicular lesion (FLUS) or atypia of undetermined significance (AUS) with Hürthle cell features (AUS/FLUS/Hürthle cell lesion of undetermined significance). The incidence of malignancy among nodules, which are cytologically suspicious for HCC, was found, by histopathology to range from 5 to 35 % [13].

In patients with a cytologic finding of AUS/FLUS, possible management strategies include repeat ultrasound-guided FNA (potentially paired with molecular testing) and close surveillance if the molecular testing is reassuring, or surgical excision for the purpose of definitive diagnosis. Molecular marker analysis in thyroid cytology has been studied predominantly in thyroid nodules with indeterminate cytology. The commercial tests for which the most data are available in validation trials are the Afirma Gene Expression Classifier (GEC, mRNA expression of 167 genes), a 7-gene panel of genetic mutation and rearrangement testing and a newer multiplexed next-generation sequencing (NGS) panel examining 400 known drivers of oncogenesis in thyroid cancer (ThyroSeq).

Molecular markers and immunohistochemistry (IHC) are promising tools in the preoperative diagnosis of HCC. Ki67 and cyclin D1 are expressed at higher levels in HC carcinomas than in HC adenoma. Bcl-2, on the other hand, is downregulated in HC carcinoma.

Other markers examined by investigators include MIB1, p53, galectin, topoisomerase II, and laminin; but, none are definitive for discrimination between benign and malignant. Sheu et al. observed that carriers of the C allele of the common C825T polymorphism in guanine nucleotide binding protein 3 gene appear to have an increased risk of developing oncocytic thyroid tumors [18]. They propose that this polymorphism may be a factor favoring the development of oncocytic thyroid tumors. Maximo et al. have recently identified somatic missense mutations in GRIM19 in approximately 11% of sporadic Hurthle cell carcinomas. GRIM19 is believed to promote apoptosis as part of the interferon and retinoic acid induced pathway of cell death, is a negative regulator of cell growth, is involved in mitochondrial metabolism, and is linked in part to mitochondrial complex I assembly Interestingly GRIM19 is located at 19p13.2 [19].

Bonora et al. have found that there are variations in the inner mitochondrial membrane transporter TIMM44 in patients with oncocytic thyroid tumors [20]. All of these studies seem to indicate that there is a genetic predisposition to develop oncocytic thyroid tumors. Ras oncogene is frequently involved in the pathogenesis of Hürthle cell tumors. In papillary thyroid cancers and in many Hürthle cell tumors, RET rearrangements are found, while these are not found in follicular tumors. Local spread may be found in RET- positive cases; RET-negative cases, as in follicular cancer cases, are more likely to spread through the bloodstream to distant metastatic sites. In 2006, Maxwell et al reported that the Hürthle cell tumors with RET/PTC positive gene arrangement have higher incidence of regional metastatic disease [21].

An association also was found between overexpression of the p53 gene product and a subset of Hürthle cell carcinomas. Isolated

studies indicate overexpression of the N-myc oncogene, tumor growth factor (TGF)-alpha, TGF-beta, insulinlike growth factor (IGF)-1, and somatostatin receptor in Hürthle cell carcinomas.

Conclusion

The presence of Hurthle cell change in a wide variety of thyroid lesions can be diagnostically challenging. However, accurate diagnosis can still be made with careful observation of the predominant cell population, nuclear features and whether there is abundant colloid or lymphocytes in the background.

Molecular markers in neoplasms show mutations either in mitochondrial DNA or in non mitochondrial genes, that interact with mitochondrial function. In nonneoplastic conditions, this mitochondrial alteration likely reflects a cellular adaptation process related to mitochondrial adaptive homeostasis.

To date, none have been definitively proven to be reliable. For now, because of the inability to determine the benign or malignant nature of such neoplasms based on molecular marker alone, a cytological approach followed by surgery is warranted.

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