Hurthle Cell Lesion: Controversies, Challenges, and Debates

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Abstract Hurthle cell lesion is one of the most questionable clinico-pathological entities in most of its aspects. Literature has used the terms oncocytic, oxyphilic, Hurthle, and Ashkanazy interchangeably; what does each term denote? Who first described these cells? What is the cell of origin? How much Hurthle cells should be present to define the lesion as Hurthle cell one? Is it possible to differentiate hyperplastic from neoplastic and benign from malignant Hurthle cell lesion on a non-histopathologic ground? Does it belong to follicular or to papillary neoplasms or should it be classified separately? Can we anticipate its clinical behavior or predict its outcome? How can we manage? We will try to answer these questions in light of the ongoing relevant arguments with the aim of resolving some uncertainties and suggesting how to solve others.

Keywords Hurthle · Oncocytic · Oxyphilic · Thyroid

Introduction

Since its description in nineteenth century to date, Hurthle cell lesion has been a subject of continuing and evolving conflicts in nearly all of its aspects, starting from its nomenclature to its management. Numerous studies, many of

which are very recent, have pointed to important facts relevant to these lesions and have proposed several clinical and non clinical tools which may help managing them. However, only few facts are established while controversies, challenges, and debates still encompass most of its spectrum. In this article, we aim to emphasize established concepts, display the ongoing arguments with a view of clarifying some uncertainties, and make suggestions which may contribute to further resolving others. In order to approach this, we reviewed the literature published in the last 20 years by using the search terms “Hurthle cell lesions” “Hurthle cell tumors” and “Oncocytic tumors” in the bibliographic database, mainly of “PubMed” and “ScienceDirect” and we retrieved 89 published manuscripts from which we constructed this narrative review.

Nomenclature Controversy: Oncocytic, Oxyphilic, Hurthle, or Ashkanazy?

An *oncocyte* is an epithelial cell defined by the presence of numerous mitochondria imparting a deeply eosinophilic finely granular appearance to the cytoplasm [1]. Mitochondrial proteins, being of basic nature, have avidity to bind acidic dyes like eosin. Because of this staining feature, oncocytes have also been termed *oxyphils*. Oncocytes have been found to arise in various tissues, including endocrine glands (thyroid, parathyroid, and pituitary glands), exocrine glands (salivary, lacrimal glands, pancreas, and liver), and secretory epithelia (nasal cavities, buccal mucosa, and larynx) [2, 3]. In the thyroid gland, these cells have also been termed *Hurthle* cells (HCs) or *Ashkanazy* cells [1, 4] after the names of these two scientists.

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Historical Controversy: Hurthle or Ashkanazy?

In 1894, Karl Hurthle talked about parafollicular cell in the thyroid of dogs [5]. The oncocytic cells derived from thyroid follicular epithelium were, in fact, first described in 1898 by Max Ashkanazy in patients with Graves' disease [6]. Despite this historical fact, the term "Hurthle cell" has continued to be used in the literature to refer to thyroid follicular cells with oncocytic features, except in Germany where the term "Askkanazy cells" is in use.

Controversy of Origin: Follicular or Parafollicular Cells?

Hurthle cells are generally thought to arise from thyroid follicular cells, based on detection of thyroglobulin immunoreactivity [7] and TSH receptor adenylate cyclase system [8]. On the other hand, parafollicular cell origin was reported [9] based on the more frequent lymphatic metastasis [10], lower radioactive iodine (RAI) avidity [11], and different oncogene expression when compared to follicular thyroid cancer (FTC) [12]. However, given that the hallmark of oncocytic change is mitochondrial proliferation as an adaptive process to a primary nuclear abnormality [4, 13], it can occur in follicular as well as in parafollicular cells [14].

Controversy of Definition: Is It a Hurthle Cell Lesion?

A Hurthle cell lesion (HCL) has been defined as a discrete lesion composed mainly of HCs. However, percentage of HCs required for the lesion to be diagnosed as HCL has been controversial. Most literature defined the lesion as HCL when oncocytes are making 75 % or more [4, 15, 16]. Some authors considered it a HCL when oncocytes exceed 50 % of follicular cells in fine-needle aspiration biopsy (FNAB) [17–19]. However, most authors used the figures 75 [20–25] and 50 % [9, 26–30] to refer to neoplastic rather than non-neoplastic HCL. Others required more than 90 % oncocytes to define the lesion as oncocytic neoplasm [26, 31].

Hurthle Cell Lesion: the Challenge of Neoplastic or Non-neoplastic?

Approximately, 15–30 % of FNA specimens are reported as "indeterminate" [32]. For these indeterminate cases in which HCs predominate, the more specific term "Hurthle cell lesion" is often reported [33]. It encompasses a variety of neoplastic as well as non-neoplastic thyroid follicular lesions. Non-neoplastic conditions in which HCs may be present include

autoimmune thyroiditis (Hashimoto's and Graves'), multinodular goiter (MNG) (with oncocytic metaplasia) as well as aging and irradiated thyroids. In such "indeterminate cases," FNAB cannot reliably diagnose neoplasia vs hyperplasia and carcinoma vs adenoma. In addition, demographic (age and sex), clinical (nodule size), and laboratory (thyroid function) data were found unhelpful to differentiate neoplastic from non-neoplastic cases [34]. Many of these pathologies may be managed conservatively if neoplasia can be excluded. Thus, a challenging clinical situation may arise if HCs are detected in FNABs. A distinction between neoplastic and non-neoplastic HCLs should be made in order to segregate patients for whom surgery is indicated from those who may be managed conservatively. Pathologists have suggested criteria to solve this challenge; abundance of HCs, dyscohesive pattern, non-macrofollicular pattern, absent or scanty colloid, and absence of background chronic inflammation are FNA features suggesting Hurthle cell neoplasm (HCN) [17, 35–37]. On the other hand, presence of HCs in cohesive flat sheets or presence of watery colloid suggests MNG with oncocytic metaplasia, while a background of lymphocytes and plasma cells usually indicates chronic lymphocytic thyroiditis [36]. Intracytoplasmic lumina and transgressing vessels may help to differentiate neoplastic from non-neoplastic HCLs with their presence favors the diagnosis of neoplastic one [17, 21, 38]. Molecular biology techniques may offer another tool; RET/PTC activation was detected in a significant number of neoplastic cases but not in hyperplastic nodules [39].

Hurthle Cell Neoplasm (HCN): the Challenge of Benign or Malignant?

The incidence of HCN varies between 3 and 10 % in all thyroid nodules [20, 22, 40]. These HCNs have been classified into Hurthle cell adenoma (HCA) and Hurthle cell carcinoma (HCC) [23]. In the absence of metastasis, a controversy arises regarding the nature of HCN as whether it is benign or malignant since cytological criteria diagnostic of malignancy, like cellular atypia and architectural distortion, may be found in benign HCNs [41]. In this context, FNAB usually reports "HCL/HCN" [1]. Moreover, intraoperative frozen section examination was consistently reported to be unhelpful [13, 27, 29, 42]. Thus, the sole distinction is based on presence or absence of capsular invasion (CI) and vascular invasion (VI) which can only be reliably identified in paraffin section. Given the aggressive behavior of histologically proven malignant HCN reported by some investigators [23], such indeterminate findings impose a challenging situation in which clinicians tend to follow a more aggressive surgical approach. However, the incidence of malignancy among nodules, which are cytologically suspicious for HCN, was found, by histopathology,

to range from 5 to 35 % [22, 27, 33]. This means that a considerable proportion of these patients is unnecessarily exposed to the risk of surgical complications. Stemming from this, investigators have tried to employ demographic (age, gender, race, ethnicity), clinico-pathological criteria (tumor size, radiation history, family history, multifocality, and coexisting thyroid pathology) to better predict the risk of malignancy in HCN. Older age was found to be significantly associated with malignancy in some studies [43, 44]; however, others found no significant association [16, 22, 45, 46]. Similarly, contradictory findings were reported concerning gender association [20, 27, 47, 48]. Larger tumors were found, by some authors, to be associated with higher malignancy rates [29, 49] while others did not find a significant association [19, 28]. Laboratory data, like preoperative thyroglobulin (Tg) concentration, were also sought; some authors found no significant difference between malignant and benign HCNs [45, 47]. However, in 2014, Petric et al. have found that preoperative Tg concentration was a predicting factor for malignancy in HCNs [50]. Similarly, sonographic criteria were investigated; hypoechogenicity [22, 46] and hyperechogenicity were significantly associated with malignancy while isoechogenicity could significantly predict benignity [46], albeit

Maizlin et al. previously found that the sonographic appearance of HCNs varied from hypo- to iso- and hyperechoic regardless of their pathology, thus precluding sonography for characterization of HCNs [25]. Literature published in the last 15 years for studies evaluating these factors is plentiful (Table 1), and it is noticeable that the discrepancy in the results is so obvious that no single factor has maintained consistency throughout all studies; this may be attributed to the retrospective and single institutional nature in all of them. This subsequently calls the need for prospective multi-institutional studies to better evaluate these factors for preoperative sorting of malignant from benign cases. In continuing trials to resolve this challenge, Arduc et al., in 2014, have found that larger body mass index and waist circumference were associated with higher malignancy risk in patients with FNAB diagnosis of HCN [51]. In addition, pathologists tried to refine the FNAB results by finding specific microscopical features; a microfollicular pattern with marked nuclear atypia in a background of HCs was found to be a significant predictor of malignancy [20]. Immunohistochemistry may provide an ancillary tool; expression of cell cycle proteins (Ki67 [24, 52] and Cyclin D1 [52]) has been shown to be significantly higher in HCC than in HCA.

Table 1 Studies evaluating demographic, clinico-pathologic, sonographic, and laboratory criteria in Hurthle cell neoplasms

Year	Author	Sample size	Significant association with malignancy?	
			Yes	No
1998	Chen et al. [29]	57	Larger tumor size	Age, gender and radiation history
1999	McHenry et al. [19]	75		Age, gender, radiation history and tumor size
2001	Sugino et al. [47]	188	Male gender	Age, tumor size and Tg concentration
2003	Lopez-Penabard et al. [43]	127	Older age and larger tumor size	Gender and radiation history
2005	Chao et al. [28]	163		Age, gender, tumor size and location
2006	Paunovic et al. [49]	199	Larger tumor size	Age
2006	Melck et al. [27]	27	Male gender and larger tumor size	Age and gland nodularity
2008	Sippel et al. [48]	57	Larger tumor size	Age, gender, radiation history, family history and presence of thyroiditis
2008	Zhang et al. [44]	55	Older age and larger tumor size	Gender and gland nodularity
2010	Pisanu et al. [20]	57	Larger tumor size and multifocality	Age and gender
2010	Suh et al. [45]	39 ^a		Age, gender, tumor size, radiation history, family history and Tg concentration
2013	Parikh et al. [46]	84	Hypo- or hyperechogenicity in the US	Age, gender, race, ethnicity, presence of thyroiditis and other sonographic criteria.
2013	Lee et al. [22]	75	Larger tumor size and hypoechogenicity in the US	Age, gender and other sonographic criteria
2014	Kroeker et al. [16]	78		Age, gender, tumor size, history of head and neck radiation, family history of thyroid cancer and calcifications in the US
2014	Petric et al. [50]	244 ^a	Male gender and higher preoperative Tg concentration ^b	Age and tumor size

^a Sample included follicular neoplasms in addition to HCNs

^b Cut-off point for serum thyroglobulin concentration is 80 ng/ml

Hurthle Cell Neoplasm: Controversies of Pathological Classification

Traditionally, HCNs have been classified into benign (HCA) and malignant (HCC) [23]. Based on histopathologic features, Erickson et al., in 2000, added a third category; HCN of uncertain malignant behavior (UMB), characterized by equivocal CI with absent VI [52]. In the same year, Cheung et al. classified HCNs into HCA, HCC, and Hurthle cell papillary carcinoma (HCPC) based on data from molecular studies [53]. In fact, demonstration of oncocyctic features in certain variants of papillary thyroid cancer (PTC) has been long recognized and reported [54]. However, the diagnosis of this entity is in itself another controversy. Some authors required the demonstration of classic nuclear features of PTC, in addition to the presence of oxyphilic cells with or without papillary growth pattern [31, 55–57]. Others necessitate the detection of a papillary architecture, with or without recognizing the diagnostic nuclear features of PTC; as these may be obscured by the nuclear hyperchromasia of HCs [15]. Recently, detection of RET/PTC rearrangement, that was thought to be specific to conventional PTC, in some HCNs has expanded the diagnosis of HCPC to include a subgroup of cancer that shows this molecular event even without detecting any of the characteristic cyto-architectural features [53, 58, 59].

Hurthle cell carcinoma has been long considered as a subgroup of follicular thyroid cancer (FTC) and was classified as such by the World Health Organization (WHO) [60] based on similar clinical behavior reported in some literature [10, 11, 61, 62]. However, stemming from the apparently more aggressive clinical behavior reported by others [63], different oncogene expression [12], and specific molecular pathogenesis [64–66], HCC has been considered by some authors to be a distinctive subset of differentiated thyroid cancer (DTC), different from FTC [23, 63, 67]. Moreover, molecular studies [53, 58, 59] have suggested that HCC would be more appropriately sub-classified under PTC [27] or at least closer to PTCs than was originally believed. However, more recently and perpetuating the enigma, data by Finely et al. have shown that the molecular signature of HCCs is most similar to FTC [68].

Based on the degree of CI and VI, HCC has been sub-classified into two groups: minimally invasive (miHCC) and widely invasive Hurthle cell carcinoma (wiHCC); however, another controversy exists in the literature concerning definition of miHCC. Chindris et al. defined it as HCC with four or less foci of CI or with less than four foci of VI [69], while Stojadinovic et al. defined it as HCC with a single focus of complete CI or a single focus of any VI or both [41]. On the other hand, Monotone opined that angioinvasion should be removed from the definition of miHCC [31]. In their series, Barnabei et al. distinguished HCC as miHCC if only CI was

reported [18] while Sanders et al. included only cases with minimal CI [11].

Two relevant concepts remain. Initially, because dedifferentiation is well documented in DTC [60], an oncocyctic poorly differentiated thyroid cancer has also been described [4, 15, 70]. Additionally, oncocyctic change can also occur in parafollicular cells resulting in oncocyctic medullary thyroid carcinoma (MTC) [71]. As a result, Sobrinho et al. stated that with the exception of undifferentiated carcinoma, every type of benign or malignant thyroid tumor has its oncocyctic variant [72]. These data support the classification system proposed by Asa [15] in which malignant HCNs are categorized into HCPC, Hurthle cell follicular carcinoma, Hurthle cell poorly differentiated carcinoma, and oncocyctic medullary carcinoma.

Controversies of Clinical Behavior

By definition, an indolent course lacking recurrence or metastasis is the clinical hallmark of benign tumors. However, for HCNs, this concept is confused by the occasional reports of recurrence or metastasis in histologically proven HCAs [73]. Asa suggested that such lesions may be unrecognized cases of HCPC [15]. To resolve this confusion, HCA has been suggested to be restricted to HCNs, not only lacking CI and VI, but also lacking RET/PTC rearrangement; HCNs showing this molecular event would be considered HCPC [58].

There has also been a considerable controversy in the literature as to whether HCC has a similar or more aggressive clinical behavior to FTC. Some authors found that they both behave in an identical fashion [61, 74] as there was no statistically significant difference between both in terms of size, extrathyroidal extension, nodal or distant metastasis, local recurrence, and patient survival [10, 11, 62, 75]. Others suggested that HCCs are more aggressive [63, 67] based on the facts of more frequent nodal [10, 76] and distal metastasis [77, 78], less RAI avidity [11, 76, 79], and greater likelihood of local recurrence [10, 23]. In a study by Shaha et al. [80], Hurthle variety categorized FTC into higher risk groups. Similarly, the clinical behavior of HCPC is controversial; some reported a behavior identical to conventional type PTC [55] while others reported a more aggressive behavior with higher rates of recurrence and cause-specific mortality [81].

Controversies of Prognosis

Age, metastasis, extrathyroid extension, and size (AMES) prognostic index, which has been long used to predict outcome of DTC, was also validated to stratify HCC into high and low risk groups and was subsequently found to correlate significantly with survival and to predict recurrence risk [11, 82]. However, as with other aspects of this tumor, controversy

is evident. Some authors found that advancing age significantly correlated with poor outcome [74] while contradictory findings were concluded by others [41, 62, 63, 83]. Similar contradiction exists regarding gender-outcome correlation [62, 63]. Likewise, larger tumor size was found to adversely impact the outcome [63, 74, 83] while others found no significant association [41, 62]. Extrathyroid extension was shown to significantly compromise survival [41, 83]; however, this was found to be insignificant in a study by Barnabei et al. [18]. With the exception of few studies [11, 18, 80], nodal metastasis was correlated with adverse prognosis [41, 63, 83] while distant metastasis always caused dismal outcome [63, 83]. The microscopic morphology appears also to correlate with outcome; in a histopathological appraisal by Stojadinovic et al. [41], all patients with miHCC exhibited a benign clinical course with no cause-specific mortality while considerable proportions of wiHCC patients developed metastasis, recurrence, or died [41], in concordance with findings reported by Sanders [11] and Chindris et al. [69]. On the other hand, Barnabei et al. stated that VI, the hallmark of wiHCC, was not associated with worse survival [18], and Goldstein et al. reported no statistically significant difference in the number of CI or VI foci between metastatic and non-metastatic HCCs [84].

Debates in Management

It is well known that surgery is an important line for managing thyroid pathologies. For HCLs, however, prudence of surgical decision, appropriateness of surgery extent, and post operative management are debatable. The first debate is whether or not to operate. Given the high incidence of malignancy in their series, Azidan et al. [85] concluded that the cytological detection of HCs in FNAB was an indication for surgery after excluding Hashimoto's thyroiditis. On the contrary, subsequent studies suggested that the percentage, rather than the mere detection, of HCs should guide the operative decision with the detection of more than 50 % HCs being an adequate criterion for opting surgery [30, 86]. The second debate is, if to operate, how much to resect. Several issues stand behind such debate. Firstly, based on the relative rarity of HCNs in general [9] and of HCCs in particular [61], single institutional experience is usually not sufficient to define an ultimate management plan. Secondly, inability to preoperatively differentiate malignancy from benignity or even to predict clinical behavior or outcome usually affect treatment decision in a way that, given a presumed aggressive nature, more radical surgery is preferable. Thirdly, most studies evaluating the outcome of surgery were retrospective studies confounded by non-matching of variables (age, gender, and tumor size) which also influence the outcome. Given the relatively small proportion of HCCs among HCN nodules and benign course identified in

most miHCC, Kroeker et al. [16], in agreement with previous reports of Parikh et al. [46], Melck et al. [27], and McHenry et al. [19], have advocated thyroid lobectomy for initial management of HCNs keeping in mind two possibilities. Firstly, proceeding to total thyroidectomy may be decided immediately if extrathyroidal extension or lymphadenopathy was detected intraoperatively. Secondly, completion thyroidectomy may be planned shortly after initial surgery if HCC was revealed on paraffin sections. Additionally, in his large series, Haigh et al. found no significant association between extent of thyroidectomy and survival [61]. On the other hand, total thyroidectomy, as an initial surgery, was supported by Mills et al. [23], Paunovic et al. [49], and Khafif et al. [62] as they noticed favorable outcomes associated with assertive resection. Moreover, a lower threshold for selecting initial radical surgery was advocated by Chen et al. [29], Sippel et al. [48], and Zhang et al. [44] in large size tumors since they detected significant correlation with malignancy. In fact, the latter opinion is fueled by several facts; the aggressive course identified in some reports [63, 67], the low avidity for RAI [11], the low incidence of complications in experienced hands [29, 49], which substantially increase in re-operative surgery, the availability of replacement therapy, the privilege of using thyroglobulin as a marker for recurrence, and the potential use of RAI for ablating a possible remnant [28]. The third debate is whether or not to use RAI. Although HCC generally fail to concentrate RAI [76], its controversial role in management is fueled by the varying results published in the literature. Lopez et al. reported a survival benefit when used for remnant ablation but not in metastatic disease [43]. On the other hand, in their series, Sanders et al. stated that using RAI did not improve outcome [11]. Moreover, Mills et al. reported a worse disease free survival (DFS) conferred by RAI ablation and therapy [23]. However, National Comprehensive Cancer Network (NCCN) 2013 guidelines have considered RAI ablation for suspected or proven thyroid bed uptake and RAI treatment for suspected or proven RAI responsive residual tumor in postoperative management of histologically proven HCC [87].

In our opinion, standardizing a management plan needs a two-pronged approach. First, starting prospectively designed randomized controlled clinical trials (RCCTs) evaluating the efficacy of different management plans on large sample of patients, which given the rarity and long natural history of the disease, would appropriately be multi-institutional. Second, employing molecular biology techniques and advanced imaging tools would resolve much of the diagnostic controversy and subsequently the management debate; for example, a recently described gene expression classifier has achieved 92 % sensitivity in detecting "suspicious" nodules which were cytologically "indeterminate" [88]. In addition, sonographic elastography scoring may contribute to better characterization of HCLs [89].

Conclusion

Despite many studies investigating HCLs in general and HCNs in particular, only few facts are established while uncertainties still obscure much of the disease spectrum. Further research, with implementation of advanced diagnostic aids and conduction of RCCTs, is needed to fix its riddle.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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