Incidental Thyroid C Cell Hyperplasia: Clinical Significance and Implications in Practice

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Introduction

Unexpected histological findings are common following surgery for thyroid diseases. A typical case is the diagnosis of thyroid cancer following thyroidectomy for presumably benign thyroidopathy [1]. Occasionally, questions regarding the optimal management can be raised when more rare pathological entities are incidentally diagnosed histopathologically following thyroid surgery. Sporadic C cell hyperplasia (CCH) is a rare clinical entity, first described by Albores-Saavedra et al. [2] in 1988, in thyroid tissue adjacent to follicular and papillary thyroid neoplasms. CCH – when encountered after thyroidectomy – may raise concerns about proper management and further therapeutic manipulations and prognosis, especially when a less than total or near-total thyroidectomy has been performed. The aim of this review is to summarize currently available data regarding the clinical significance and optimal management of patients with incidentally diagnosed sporadic CCH.

Definition – Diagnosis

Incidental C cell hyperplasia (CCH) following thyroidectomy for other indications may rarely be encountered, which may raise concerns about its clinical significance and proper management. CCH can be classified as physiological (reactive) or neoplastic. Reactive CCH has no malignant potential and can be observed in association with many other thyroid diseases (including differentiated thyroid cancer); in contrast, neoplastic CCH should be considered as a preneoplastic stage in the spectrum of C cell disease, ultimately leading to the development of medullary thyroid cancer (MTC). Neoplastic CCH is commonly observed in patients with germ-line mutations in the \textit{RET} oncogene (commonly in families with a history of hereditary MTC, i.e. familial MTC or multiple endocrine neoplasia type 2 (MEN2)). CCH should be considered in patients with hypercalcitoninemia without nodular thyroidopathy. Total thyroidectomy, which is commonly performed for the majority of thyroid diseases, is an adequate treatment and achieves cure, even in patients with neoplastic CCH. There is no role for cervical lymph node dissection in patients with pure CCH. In conclusion, reactive CCH has no malignant potential, in contrast to neoplastic CCH. Total thyroidectomy achieves cure of patients with CCH.

Keywords

Thyroid · Surgery · Neoplasms · Tumors · Hyperplasia · C cells · Parafollicular cells · Thyroidectomy · Cervical lymph node dissection

Summary

Incidental C cell hyperplasia (CCH) following thyroidectomy for other indications may rarely be encountered, which may raise concerns about its clinical significance and proper management. CCH can be classified as physiological (reactive) or neoplastic. Reactive CCH has no malignant potential and can be observed in association with many other thyroid diseases (including differentiated thyroid cancer); in contrast, neoplastic CCH should be considered as a preneoplastic stage in the spectrum of C cell disease, ultimately leading to the development of medullary thyroid cancer (MTC). Neoplastic CCH is commonly observed in patients with germ-line mutations in the \textit{RET} oncogene (commonly in families with a history of hereditary MTC, i.e. familial MTC or multiple endocrine neoplasia type 2 (MEN2)). CCH should be considered in patients with hypercalcitoninemia without nodular thyroidopathy. Total thyroidectomy, which is commonly performed for the majority of thyroid diseases, is an adequate treatment and achieves cure, even in patients with neoplastic CCH. There is no role for cervical lymph node dissection in patients with pure CCH. In conclusion, reactive CCH has no malignant potential, in contrast to neoplastic CCH. Total thyroidectomy achieves cure of patients with CCH.
Moreover, C cell densities differ between men and women (male/female > 2) and vary according to age and even between 2 individuals of the same age [6, 7].

The definition of CCH is complicated by the difficulty in estimating the total number of C cells within the normal thyroid gland; the added difficulty in defining what is 'normal' and what represents 'hyperplasia' further complicates the matter [9]. Some groups tried to document the normal C cell population in the thyroid gland in necropsy studies [10–13]. Albores-Saavedra et al. [2] found that, in previously healthy subjects who died suddenly, the number of C cells at a magnification of 100 × ranged from 0 to 42. This group proposed that, to establish the diagnosis of CCH, at least 50 cells must be present in at least 1 low-power field (× 100; LPF), a number greater than that found in most normal subjects [4, 14]. Wolfe et al. [15] reported a wider range, which included 3 cases showing densities of > 1,000 cells/mm³. Such densities usually corresponded to a maximum well over 100 cells per 10 × field. Guyénot et al. [16] observed an increase in C cell density as CCH progressed from focal to diffuse and from diffuse to nodular subtypes.

CCH can be easily overlooked as it can be subtle or unapparent in hematoxylin and eosin (H&E)-stained sections because of the morphological similarity between C cells and adjacent follicular cells [6, 17]; histopathological diagnosis requires calcitonin immunostaining. However, in clinical practice, calcitonin staining is not routinely used in the absence of a prior consideration of a C cell disorder. The methodology to diagnose CCH varied from one study to another and, because the choice of the thyroid site examined and the extent in sampling have a direct bearing on the C cell density, this prevents any relevant comparison of the results of these studies. Furthermore, there are nearly as many units used to quantify C cells or to assess CCH as there are studies, increasing the difficulty of any comparison. C cell density has been measured as the number of cells per follicle, per cluster, per LPF, per millimeter squared or cubed, and in many other ways [9].

Preoperatively, diagnosis should be suspected in the presence of hypercalcitoninemia. Apart from MTC, CCH is the most common feature found in patients with hypercalcitoninemia, especially in the absence of suspected thyroid nodules (which could indicate the presence of MTC). Some groups tried to define cut-off values for basal and stimulated calcitonin levels to diagnose CCH and differentiate hyperplastic CCH from MTC [8, 18]. Verga et al. [8] found that serum calcitonin levels > 50 pg/ml were always associated with CCH, without correlation between calcitonin levels and the number of C cells or the final diagnosis. Jacobone et al. [18] proposed that values for basal calcitonin levels > 30 pg/ml, reactive stimulated calcitonin levels > 200 pg/ml, or both are considered as findings highly predictive of MTC. These authors concluded that basal calcitonin levels < 30 pg/ml along with stimulated calcitonin levels < 200 pg/ml cannot be used to differentiate between CCH and MTC [18]. The clinician, however, should acknowledge that normal basal calcitonin levels do not exclude CCH or micro-MTC and cannot be used to distinguish between physiological and neoplastic CCH on quantitative grounds [16].

### Classification

CCH has been classified as physiological/reactive or neoplastic [17].

**Reactive CCH**

Reactive CCH has been reported in newborns, in the elderly, and in patients with hyperparathyroidism, Hashimoto’s thyroiditis, previous hemithyroidectomy, and follicular thyroid adenomas and carcinomas, lymphomas, papillary carcinomas, but also non-thyroid disease (such as hypergastrinemia due to Zollinger-Ellison syndrome, exogenous estrogen administration, hypercalcemia/hyperparathyroidism, and cimetidine treatment) [7, 10, 16, 19–25]. Scopsi et al. [26] found that CCH is diagnosed in 30% of pathological thyroid glands. This group observed that the proportion of somatostatin (SMS) antibody-immunoreactive C cells increased from about 1% of calcitonin-immunoreactive cells in normal adult thyroid glands to 2.5% in follicular adenomas, 3% in follicular carcinomas, 4.6% in papillary carcinomas, and 5.7% in metastases [26]. Reactive CCH can be classified – according to the growth pattern of C cells – as focal, diffuse, or nodular [17, 27]. The incidence of CCH in thyroid tissue adjacent to follicular cell tumors is significant (35–50%) [2, 19]. The incidence of putimoral CCH is further increased in patients with radiation-induced epithelial thyroid tumors than adjacent to sporadic thyroid tumors [28]. An iodine-deficient diet or propylthiouracil administration could be accompanied by an increase in calcitonin levels, suggesting a potential role of thyroid-stimulating hormone (TSH) in C cell regulation [19]. Reactive CCH may result through an immunopathological mechanism or via an effect of the inflammatory mediators and cytokines secreted by the infiltrating inflammatory cells in the thyroid parenchyma [19]. There is evidence suggesting the involvement of a functional interconnection between follicular and parafollicular C cells [28]. A thyroid pathology (such as a follicular or papillary thyroid neoplasm) may cause the destruction of thyroid parenchyma, leading to chronic TSH oversecretion, which stimulates both follicular and C cells [2]. The role of C cell growth factors, such as the gastrin-related peptide whose gene is overexpressed in hyperplastic C cells adjacent to follicular cell tumors, has also been suggested [29]. Guyénot et al. [19] suggested the possible role of overexpression, in thyroid cancers, of paracrine growth factors influencing the surrounding C cells or, alternatively, in hyperplastic C cells, of a growth factor favoring the hyperplastic and/or neoplastic transformation in the adjacent follicular cells.

Diagnosis of reactive CCH requires calcitonin immunostaining and quantitative analysis to be identified with certainty (see Definition – Diagnosis); otherwise, it can be easily overlooked (in H&E-stained sections) because of the similarity between C cells and adjacent follicular cells [6, 17] (see above). Reactive CCH has no documented malignant potential (see below) and it is not associated with sporadic MTC [17, 30].
Neoplastic CCH

Neoplastic CCH is characterized by the presence of large, mildly to moderately atypical, round, polygonal or spindle-shaped cells with nuclear pleomorphisms [17] (see also: WHO Classification of Tumors of Endocrine Organs) [31]. These cytological alterations allow the C cells to differentiate from the follicular cells and therefore to diagnose neoplastic CCH even based on H&E-stained sections (while the reactive type usually would require immunohistochemistry (IHC) for its identification, as noted above). Several other terms have been proposed to describe neoplastic CCH, including 'in situ MTC', 'thyroid intraepithelial neoplasia of C cells', 'C cell intraepithelial neoplasia' (CCIN) [27, 32], etc.

Neoplastic CCH is considered as a preneoplastic condition in patients with germ-line mutations in the RET oncogene and is usually associated with hereditary MTC (familial MTC or multiple endocrine neoplasia type 2 (MEN2)) [32, 33]. In these cases, CCH has been considered as a different state in C cell pathology [27, 34–36]. It is especially important (from a clinical perspective) to emphasize the clinical significance of prophylactic thyroidectomy at the CCH stage based on the finding of specific RET mutations, thereby preventing the development of hereditary MTC and dramatically improving prognosis [37]. However, neoplastic CCH may also precede the development of sporadic MTC in the absence of germ-line RET mutations [17, 33, 34, 38]. Scheuba et al. [35] have identified neoplastic CCH in 15/39 sporadic CCH cases; Kaserer [34] has reported the presence of neoplastic CCH in association with sporadic micro-MTC in 6/34 cases. Guyévant et al. [16] found neoplastic CCH in 10/14 (71.4%) MEN2 cases, but also in 8/46 (17.4%) sporadic cases. These findings suggest that neoplastic CCH could also be the precursor of some sporadic MTCs. The absence of CCH in the thyroid parenchyma of all patients with sporadic MTC suggests that this pathological entity may result from other alternative pathways not requiring a neoplastic CCH stage [16]. Of note, the criteria to identify the lower limit of microinvasive MTC and the upper limit of CCH are still being debated [32].

Differentiating accurately between reactive and neoplastic CCH is not always possible, given that both reactive and neoplastic C cells may have an extremely variable phenotype [27, 32, 39]. The value of bilaterality as a criterion in favor of neoplastic CCH is considered as a different state in C cell pathology [27, 34–36]. As is well known, in familial MTC, CCH is classically bilateral and represents a preneoplastic stage, with natural progression to MTC [32]. For a long time, the coexistence of CCH and MTC within the thyroid parenchyma has been considered as an indicator of MEN2 [42] and CCH has been viewed as a preneoplastic stage of C cell disease (neoplastic CCH, see above) [28]. The progression from CCH to MTC has been recognized as a well-defined event in the familial setting, including familial MTC and MEN2 syndrome [32, 38, 43]; thus, recognition of specific genetic changes allowed prophylactic thyroidectomy to be performed at an early stage of this evolution, thereby preventing the progression of the C cell disease to MTC [37].

Sporadic CCH as an incidental finding in patients with another underlying thyroid pathology has a different biological behavior. In this clinical setting, CCH is considered as a reactive proliferation of C cells; it lacks specificity as a MEN2 predictor and should not be considered as a preneoplastic lesion [2, 7, 16, 18, 44]. Based on currently available data, sporadic CCH may represent a physiological or reactive proliferation of calcitonin-producing cells in response to different physiological and/or pathological endocrine stimuli (e.g., TSH overstimulation, hypercalcemia, and paracrine factors) or a neoplastic lesion affecting follicular cells [14, 30, 38].

The astute clinician should suspect CCH in patients with increased calcitonin levels and in the absence of dominant thyroid nodule(s). Total thyroidectomy (which is currently the preferred surgical approach in the majority of thyroid diseases, including thyroid cancer) is the procedure of choice for patients with CCH. The detection of specific RET mutations in the appropriate clinical setting should be considered as an indication for prophylactic total thyroidectomy, a procedure that offers the possibility to resect the at-risk thyroid parenchyma at the CCH (preneoplastic) stage prior to the development of MTC, thereby achieving cure of the patient from a potentially lethal disease [37]. There is no role for cervical lymph node dissection in patients with pure CCH.

Clinical Significance and Management

As is well known, in familial MTC, CCH is classically bilateral and represents a preneoplastic stage, with natural progression to MTC [32]. For a long time, the coexistence of CCH and MTC within the thyroid parenchyma has been considered as an indicator of MEN2 [42] and CCH has been viewed as a preneoplastic stage of C cell disease (neoplastic CCH, see above) [28]. The progression from CCH to MTC has been recognized as a well-defined event in the familial setting, including familial MTC and MEN2 syndrome [32, 38, 43]; thus, recognition of specific genetic changes allowed prophylactic thyroidectomy to be performed at an early stage of this evolution, thereby preventing the progression of the C cell disease to MTC [37].

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Disclosure Statement

The authors of this paper certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
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