ORIGINAL ARTICLE

C-cell hyperplasia in sporadic and familial medullary thyroid carcinoma

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ABSTRACT

Context: C-cell hyperplasia (CCH) is characterized by increased mass of C-cells and has been identified as a precursor condition for medullary thyroid carcinoma (MTC). Varying proportion of MTCs is associated with CCH in different studies. This could be due to the lack of uniformity of the definitions and techniques used to identify CCH in these studies. **Aims:** This study aims to study the occurrence, clinicopathological, and immunohistochemical features of CCH in MTC diagnosed during a 22-year period at a tertiary care center in North India and to review the available literature on CCH. **Materials and Methods:** Eighty-seven consecutive cases of MTC were included in the study. Histological evaluation for the presence of CCH and neoplastic CCH was performed. Confirmation of CCH was done by immunohistochemistry for calcitonin and chromogranin. The presence of neoplastic CCH was correlated with clinical factors and prognostic factors. **Results:** Of 87 cases of MTC included in the study, 71 (82%) patients were sporadic and 16 (18%) had familial MTC. Neoplastic CCH was seen in 12 (75%) familial and in 9 (13%) sporadic MTC. Patients with familial MTC were more frequently associated with neoplastic CCH than sporadic MTC ($P < 0.001$), were younger ($P < 0.001$), and had more often bilateral and multifocal tumors ($P < 0.001$). However, there was no significant difference in mean survival time and progression-free survival in patients with and without CCH. **Conclusion:** CCH, though more common in familial MTC, can also be seen in sporadic tumors. CCH is not associated with patient survival and disease progression.

KEY WORDS: C-cell, familial, medullary, sporadic

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INTRODUCTION

Medullary thyroid carcinoma (MTC) is a relatively uncommon malignant thyroid tumor composed of cells showing evidence of C-cell differentiation. It accounts for 3%–10% of all thyroid malignancies and can occur sporadically or in familial forms. The familial forms account for about 25%–30% cases of MTC and show an autosomal-dominant mode of inheritance.[1,2] MTC accounts for about 13% of all thyroid cancer-related deaths with an overall survival rate and prognosis intermediate to that of patients with differentiated thyroid cancer and anaplastic thyroid cancer.[3,4]

C-cells, the calcitonin-secreting cells in thyroid, form a minor cell population, comprising only 0.1% of the glandular mass of the thyroid.[5] C-cell hyperplasia (CCH) is a proliferative condition characterized by an increased mass of C-cells within the follicles of the thyroid gland and has been identified as a precursor condition for MTC. Varying proportion of MTCs is associated with CCH; the incidence varying between 60%–80% in familial and 40%–50% in sporadic MTC in different studies.[6,7] This could be due to the lack of uniformity of the definitions and techniques used to identify CCH in these studies. CCH has been noted in Indian studies on MTC but not discussed elaborately.[8] We studied the occurrence, clinicopathological, and immunohistochemical features of CCH in familial and sporadic MTC diagnosed during a 22-year period at a tertiary care center in North India. This is probably one of the largest studies on CCH in MTC in world literature and the first from the Indian subcontinent.

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MATERIALS AND METHODS

Eighty-seven consecutive cases of MTC diagnosed at the Department of Pathology, SGPGIMS, Lucknow, India, between January 1991 and December 2012 were included in the study. Clinical details including family history of thyroid tumor, physical and radiological examination, biochemical parameters including serum calcitonin levels, result of mutational analysis when performed, and follow-up data were retrieved from the hospital records.

Gross features of the thyroid specimens received were recorded, and adequate sections were included from the tumor and from nonneoplastic thyroid.[1] Wherever possible, sections were included from the upper two-thirds of lateral lobes of thyroid where the concentration of C-cells is reported to be the highest.[5] Hematoxylin and eosin stained slides of all cases were reviewed, and histological features of the tumor and presence and type of CCH were recorded. Immunohistochemistry (IHC) was performed in all the cases for calcitonin and chromogranin. A diagnosis of CCH was made when at least three low-power fields containing ≥50 calcitonin immunostained C-cells were observed.[6] The growth patterns of CCH were described as focal CCH, corresponding to a segmental proliferation within the follicle; diffuse CCH as a C-cell proliferation forming a circumferential intrafollicular collar which pushes the follicular cells toward the lumen; and nodular CCH when C-cell clusters obliterate the follicular lumen completely.[9,10] Neoplastic CCH was diagnosed by the presence of clusters of C-cells showing at least mild atypia with nuclear pleomorphism, differing from adjacent follicular cells and resembling those identified in a medullary carcinoma.[9] Progression-free survival was defined as the absence of overt locoregional or distant metastasis after primary surgery.

RESULTS

Of 87 cases of MTC included in the study, 71 (82%) patients were sporadic and 16 (18%) had familial MTC; all familial MTC had clinical features of multiple endocrine neoplasia (MEN) 2A. The results of mutational analysis were available in nine patients of MEN syndrome. Eight patients showed codon 634 mutation on exon 11, and one patient showed codon 804 mutation on exon 14 of rearranged during transfection proto-oncogene.

The mean age of the patients with MTC was 42.6 ± 15.5 years (range 12–77 years). The mean age of presentation in males and females was 45.5 ± 14.5 years and 39.1 ± 16 years, respectively. In sporadic MTCs, males (n = 44, 62%) outnumbered females (n = 27, 38%) by a male:female ratio of 1.6:1. In familial MTC, females (n = 9, 56%) marginally outnumbered males (n = 7, 44%) by a male:female ratio of 1:1.3. All the patients of sporadic and 81% (16) of familial presented as neck mass. Other features seen less commonly were neck pain, dysphagia, hoarseness of voice, diarrhea, loss of appetite and weight, hypertension, palpitation, and abdominal pain.

Neoplastic CCH was seen in 12 (75%) familial and in 9 (13%) sporadic MTC [Table 1]. Of these, nodular neoplastic CCH [Figure 1a and b] was seen in 7 (44%) familial and 5 (7%) sporadic MTCs. Focal neoplastic CCH was seen in 31% (n = 5) of familial and 6% (n = 4) of sporadic MTC. However, the morphological variants were not mutually exclusive, and some focal hyperplasia was also seen in cases with nodular hyperplasia [Figure 2a and b]. In all cases, CCH was located adjacent to tumor. CCH was differentiated from infiltrating carcinoma by the absence of infiltration of the interstitium, absence of associated stromal desmoplasia, and absence of amyloid deposits. It was bilateral in three patients with familial carcinoma and was confirmed by strong calcitonin immunoreactivity. Patients with familial MTC were significantly younger than patients with sporadic MTC ($P < 0.001$), had more often bilateral and multifocal tumors ($P < 0.001$), and were more frequently associated with neoplastic CCH ($P < 0.001$) [Table 2].

The difference in mean survival time in patients of MTC with CCH (79.6 ± 14.7 months) and without CCH (318.7 ± 33.7 months) was not significant. Similarly, the difference in progression-free survival between patients of MTC with or without CCH was not significant.

DISCUSSION

We studied the incidence of CCH in sporadic and familial MTC and found neoplastic CCH in 75% of familial and in only 13% sporadic MTCs ($P < 0.001$). Patients with familial MTC were significantly younger than sporadic MTC ($P < 0.001$) and more often had bilateral and multifocal tumors ($P < 0.001$). There was no other significant difference between familial and sporadic tumors in relation to clinical, histological, immunohistochemical features, and survival.

These findings are largely similar to other studies.[6,11] In the study by Kaserer *et al.*, hereditary MTC was significantly associated with younger age, multifocal disease, bilateral involvement, desmoplastic stroma, and presence of CCH.[11] Although these factors are preferentially associated with hereditary tumors, they may also be seen in some sporadic tumors and therefore may not be of value in an individual patient.

In the normal gland, C-cells occur singly or in small groups of 3–5 cells and have an intrafollicular position.[12,13] Electron

Table 1: Histological features of C-cell hyperplasia in medullary thyroid carcinoma

C-cell hyperplasia	*Sporadic MTC (n=71)*	*Familial MTC (MEN 2A) (n=16)*
Number of patients (%)	9 (13)	12 (75)
Type of hyperplasia		
Nodular	5	7
Focal	4	5
Bilateral	0	3
Cytologic atypia	9	12

MEN 2A: Multiple endocrine neoplasia, type 2A; MTC: Medullary thyroid carcinoma

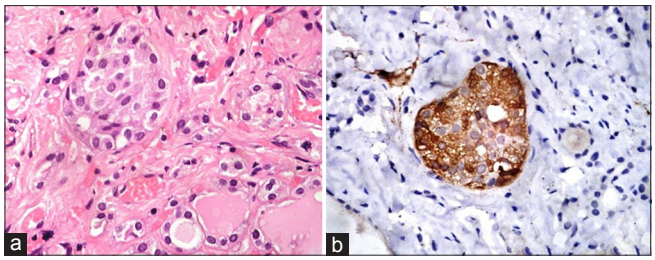

Figure 1: Nodular neoplastic C-cell hyperplasia: (a) C-cells filling the follicular lumen and displaying slightly larger nuclei with granular cytoplasm, as compared to adjacent follicular cells (H and E, ×400); (b) calcitonin (immunostain, ×400)

Table 2: Clinicopathological differences between sporadic and familial medullary thyroid carcinoma

Clinicopathological features	*Sporadic MTC (n=71), n (%)*	*Familial MTC (n=16), n (%)*	*P*
Age (years) (*n*=87)	46.1±14	27.6±14	<0.001
Males	44 (62)	7 (44)	
Females	27 (38)	9 (56)	
Neoplastic C-cell hyperplasia	9 (13)	12 (75)	<0.001
Multifocal (*n*=80)	20 (31)	14 (88)	<0.001

MTC: Medullary thyroid carcinoma

microscopy demonstrates their intrafollicular position and the presence of two main types of secretory granules, both containing calcitonin.[5] Histological clues for identification of C-cells include larger and more granular nuclei and clear or lightly staining cytoplasm, as compared to adjacent follicular cells. C-cells show argyrophilia detected by positivity in Grimelius stain. On IHC, the most specific marker for C-cells is calcitonin. Other neuroendocrine markers such as chromogranin A, synaptophysin, and neuron-specific enolase are also expressed.[5]

CCH has been identified as a preneoplastic lesion of MTC and terms such as C-cell disease and carcinoma *in situ* were also proposed.[14,15] The exact number of C-cells is unknown, and for this reason, it is difficult to define a true CCH.[16] A definition of CCH is the presence, in at least one area with the highest estimated C-cell density, of more than 50 immunostained C-cells per one low-power field (×100 magnification) in both thyroid lobes.[11,16,17] Guyétant *et al.* defined CCH as more than 40 C-cells per square centimeter or more than 50 calcitonin-positive C-cells found in three low-power fields (×100 magnification).[6] However, these studies do not show any correlation with serum calcitonin.

CCH is also classified as reactive and neoplastic. Reactive or physiologic increase has been described in neonates, elderly, hyperparathyroidism, hypergastrinemia, lymphocytic thyroiditis, and in peritumoral locations.[10] Neoplastic CCH is a genetically defined event, considered to be the precursor lesion of MTC in familial and few sporadic MTC.[1,18] The terms reactive and neoplastic CCH are not uniformly accepted by all workers due to overlapping features and problematic differentiation on histology. Guyétant *et al.* in a morphometric study of C-cells in normal thyroids show that 33% of adult individuals fulfill the criteria of CCH.[19] Our study defines neoplastic CCH similar to Perry *et al.*

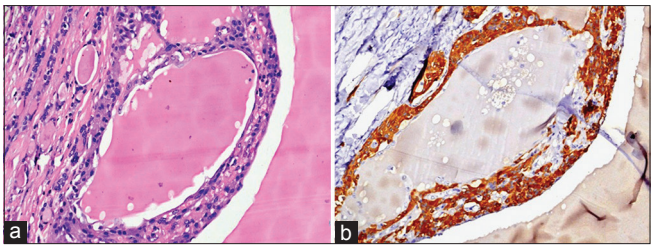

Figure 2: (a) Neoplastic C-cell hyperplasia arising at parafollicular location, adjacent to medullary thyroid carcinoma (not in picture) (H and E, ×200). (b) Calcitonin (immunostain, ×200)

Unlike physiologic CCH, neoplastic C-cells have mild-to-moderate cytological atypia, nuclear pleomorphism, similar to those of invasive MTC, and are recognizable in routine stains (HE) while reactive CCH cannot be identified without the help of IHC.[6,9,11] Therefore, the numerical definitions regarding neoplastic CCH seem virtually irrelevant. Komminoth *et al.* have suggested that positive immunostaining for expression of polysialic acid (a posttranslation modification of neural cell adhesion molecule) supports a diagnosis of neoplastic CCH, but this feature is also not absolutely specific.[20]

Progressive increase in proliferation index accompanied by increase of molecular alterations and monoclonality in CCH is thought to lead to medullary carcinoma.[21] The term medullary microcarcinoma is defined if it is <1 cm in greatest dimension and has invaded the follicular basement membrane. Distinction of CCH from microinvasive medullary carcinoma may be difficult. The presence of fibrosis around tumor cell nests and demonstration of defects in the follicular basement membrane support the diagnosis of MTC.[21] CCH also needs to be differentiated from intrathyroidal spread of medullary carcinoma and solid cell nests, which are intrafollicular aggregates of cells resembling squamous or transitional epithelium and considered as remnants of ultimobranchial bodies. The solid cell nests are usually not immunoreactive for calcitonin.[22]

A finding of CCH has been considered to be indicator of MEN 2 syndrome, but it may also be seen in sporadic cases and may not be of importance in an individual case for differentiating familial cases from sporadic.[6] Although we also observed CCH in sporadic MTC, the unavailability of mutational analysis in our study precludes a definitive argument supporting the occurrence of CCH in sporadic MTC. Recent increase in prophylactic thyroidectomies performed at an early age, especially in patients with mutations in codons carrying a high risk of development of MTC or due to raised serum calcitonin levels, may have resulted in increase in the cases with isolated neoplastic CCH or microcarcinoma; thus, understanding of its morphology is required for diagnosis of CCH.

CONCLUSION

CCH is a multifocal proliferative condition characterized by an increased mass of C cells within the follicles of the thyroid gland. The most accepted definition of CCH is the presence,

in at least one area with the highest estimated C-cell density, of more than 50 immunostained C-cells per one low-power field (×100 magnification). Neoplastic C-cells have mild to moderate cytological atypia, similar to those of invasive MTC, and so the numerical definitions regarding neoplastic CCH seem virtually irrelevant. CCH has been considered to be an indicator of familial MTC, but it may also be seen in sporadic cases and is not significantly associated with survival and disease progression.

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Conflicts of interest

There are no conflicts of interest.

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