Immunohistochemical study on the location of C cells

Kafeel Hussain[1,*], Swayam Jothi[2]

[1]Assistant Professor, [2]Professor & HOD, Dept. of Anatomy, Shri Sathya Sai Medical College & Research Institute, Nellikuppam, Tamil Nadu

***Corresponding Author:**
Email: akafeelhussain@gmail.com

Abstract

Introduction: C cells have been predominantly documented to be parafollicular in position in the thyroid. However, C cells have also been reported to occur in the interfollicular space, but this has also been attributed to misinterpretation of tangential sections.
Aim: To study the location of C cells in normal and pathological conditions of the thyroid.
Materials and Method: Immunohistochemical study using calcitonin rabbit polyclonal antibody was performed in a total of 191 thyroid specimens (38 normal, 44 multinodular goiter, 31colloid goiter, 42 papillary carcinoma(Ca.) thyroid and 36 Hashimotos thyroiditis).
Observation: In all the normal and pathological conditions of the thyroid, which showed C cells but with no overt C cell hyperplasia(CCH), the C cells were found parafollicular in position. However, there were instances where C cells were also found well within the colloidal lumen, as in 2 cases of colloid goiter. C cells were predominantly parafollicular/ intrafollicular in all cases exhibiting CCH with the exception that interfollicular nodular C cell proliferations were observed in a case of papillary Ca. thyroid and a case of Multinodular goitre.
Conclusion: C cells always are in their native intra or parafollicular position in normal states and predominantly tend to remain so in hyperplastic states as well. However, in certain hyperplastic conditions, they can also form nodules that appear in the interfollicular space or interstitium. C cells can rarely also be found in the colloidal lumen. Such cells could possibly derive their origin from stem endodermal cells and thereby possess an inherent ability to traverse the basement membrane.

Keywords: Interfollicular, Parafollicular, CCH, Stem endodermal cells.

Received: 18th July, 2017 **Accepted:** 4th August, 2017

Introduction

The thyroid parenchyma presents two cell populations both distinct in their morphology and function. The follicular cells are more numerous and synthesize thyroglobulin, and the C-cells, the minor cell population, also known in the past as parafollicular cells secrete calcitonin. The first evidence for the existence of a second type of epithelial cell in the mammalian thyroid gland was provided by Nonidez and interpreted their position as being parafollicular. However. C cells have also been reported to occur in the interfollicular space, but this has also been attributed to misinterpretation of tangential sections. Electron microscopic studies have shown that the C cells are separated from the interstitium by the follicular basal lamina and from the luminal colloid by extensions of the follicular cell cytoplasm. However reports of C cells in the colloidal lumen also exist. Moreover, extension of C-cells through defects in the follicular basal lamina and their infiltration into the thyroid interstitium is deemed as the malignancy criteria (De Dellis)[(1)] in differentiating between CCH and early micro-Medullary Thyroid carcinoma(MTC).

Aim

To study the location of C cells in normal and pathological conditions of the thyroid.

Materials and Method

A total of 191 thyroid specimens (38 normal, 44 multinodular goiter, 31colloid goiter, 42papillary ca thyroid and 36 hashimotos thyroiditis) were used in this study. The normal thyroid glands of the cadavers and the pathological specimens of the thyroid gland were procured from the Dept. of Anatomy and Pathology of SSMCRI and MGMCRI. Immunohistochemical study using calcitonin rabbit polyclonal antibody was performed to identify the C cells. The criteria for identifying C Cell hyperplasia was more than 50 calcitonin positive cells found in three low-power fields (×100 magnification).[(2)]

Exclusion criteria: Care was taken to exclude-

- Glands with autolytic alterations due to excessive time between death and fixation.
- Any gross or histopathological evidence of Thyroid diseases (tumour or goitre) in normal Thyroid glands.

Observation

C cell hyperplasia was not encountered in any of the normal thyroid specimens. However, C cells were evident in all the **normal** cases. Amongst the 153 cases of **various thyroid diseases** examined, C cell hyperplasia was encountered in 33 cases (21.56%) and 23 cases (15%) showed no evidence of any C cells. The

list of the individual pathological conditions are in Table 1.

Table 1: C cells in the various pathological conditions of the thyroid

Pathology	Total no. of cases	CCH	C Cells present but not satisfying criteria for CCH	C cells undetected
Colloid goitre	31	0	29	2
CLT	36	19	14	3
Papillary Ca.	42	1	34	7
MNG	44	13	20	11
total	153	33	97	23

In all the normal and pathological conditions of the thyroid, which witnessed the presence of C cells but with no overt C cell hyperplasia, the C cells were found either singly or in small parafollicular groups of 5-6 (Fig. 1) No C cells were ever found in an interstitial or interfollicular location in them. Interestingly, however there were instances where C cells were also found well within the colloidal lumen as in 2 cases of colloid goiter(Fig. 3 a and b).

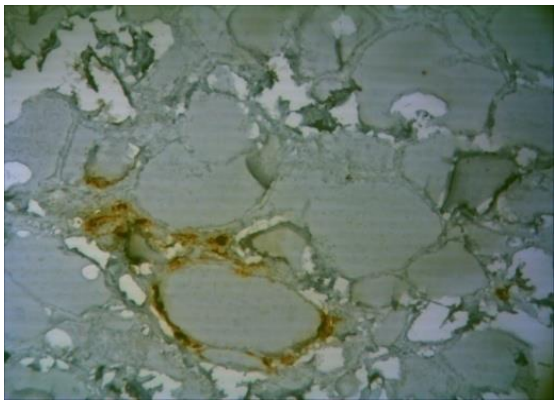


Fig. 1: C Cells parafollicular in location

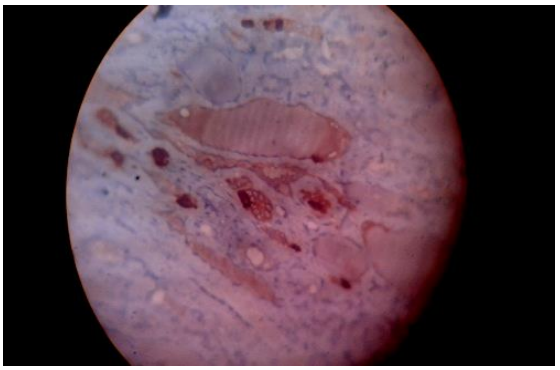
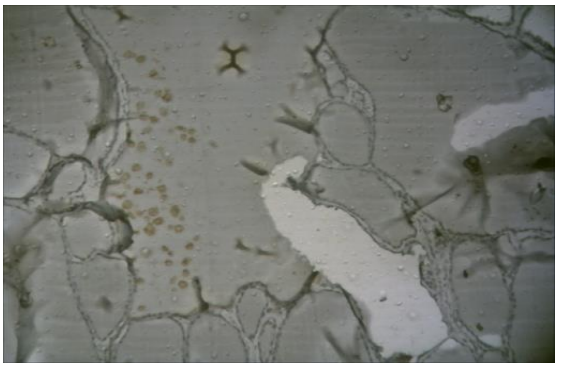
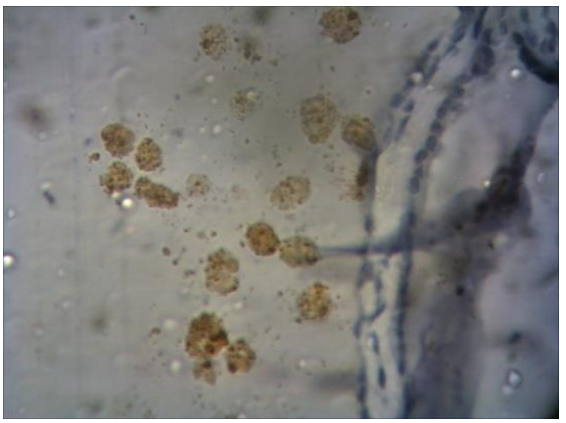


Fig. 2: Physiological nodular CCH in the normal thyroid (10x) tissue adjacent to Papillary Ca. (40X)

C cells were predominantly parafollicular /intrafollicular in all cases exhibiting C Cell hyperplasia. This intrafollicular relationship was maintained even in a hyperplastic scenario with the exception that interfollicular C cells in the form of nodular proliferations were observed in a case of papillary Ca. thyroid (Fig. 2) and in a case of Multinodular goitre.



a) **10X**



b) **100X**

Fig. 3: C cell well within the colloidal lumen in colloid goitre

Discussion

C-cells have been reported to occur in clusters in the interfollicular space, but individual studies conducted by Bussolati et al., 1967;[3] Carcangiu, 1997[4] and LiVolsi, 1990[5] made them conclude that this could result from misinterpretation of tangentional sections of the follicles in light microscopy.

In the present study, C cells were not evident in 23 thyroid specimens of various pathologies. Studies by Gmünder-Lehner[6] pointed out that C-cells were sometimes not found in the entire thyroid at all.

In the current study, C cell nodules which appeared in the interfollicular space, in a case of papillary Ca and Multinodular goitre were a physiological hyperplastic response. Apel et al.[7] also reported adenomatous or hyperplastic nodules in multinodular goiter which were benign and did not develop a malignant clinical courses. Also, in C Cell hyperplasia, when C cell numbers increase, C cells occasionally appear in the interfollicular space forming nodules.

Kracht et al. 1969[8] found that the C cell hyperplasia encountered in hyperparathyroidism presented as "knots and clusters" and the individual C cells were hypertrophied. These C cells surrounded some of the follicles and even replaced the follicular cells. Serge Guyetant et al, 1997(9) documented that when density of C cells grew, C cells were identified in an increasing number of sections, partially replacing the follicular epithelial border and the colloid lumen

Animal studies conducted in bats by Nunez E. A et al, 1967[10] and Azzali, G., 1968[11] and in rats by Wissing, S.L, 1962[12] and Ekholm et al, 1968[13] ultra-structurally demonstrated that both normal and hyperplastic C-cells occupied an intrafollicular localization, being separated from the interstitium by the follicular basal lamina and from the luminal colloid by extensions of the follicular cell cytoplasm. DeLellis RA, Nunnemacher G, Wolfe HJ (1977)[1] confirmed the same in human thyroids.

Textbooks in histology have often stated that C cells do not reach the colloidal lumen. However Radivoj V. Krstic[14] had stated that C cells are occasionally found in follicular lumen. However, he never gave explanations as to why or how they come into the lumen.

The most widely accepted explanation for tumor cell invasion and metastasis is “the three-step hypothesis of invasion”. The first step of which is tumor cell attachment to the ECM (extra cellular membrane) followed by proteolytic degradation of the ECM (due to advancing pro-truding actin-rich pseudopods) leading to the migration of the tumor cell body through the remodeled matrix.

According to Lance A. Liotta, 2016[15] the same three-step mechanism is used during non-neoplastic physiologic invasion. Normal adult stem cells also leave the bone marrow, extravasate, intravasate, and colonize distant tissue, a phenotype that is identical to cancer metastasis.

According to Albores-Saavedra et al., 1990,[2] Harach, 1997[16] and Papotti et al., 2000,[17] “stem endodermal cells” could be the origin of a minor subset of C-cells.

This creates a room for accommodating the possibility that Normal C cells, which derive their origin from stem endodermal cells could possess the ability to traverse the basement membrane and could explain the observations of the presence of C cells well within the colloidal lumen. However, the difference between physiologic and malignant invasion is that physiologic invasion stops after entry. Incontrast, tumor cells invade relentlessly.

Conclusion

C cells always are in their native intra or parafollicular position in normal states and predominantly tend to remain so in hyperplastic conditions as well. However, in certain hyperplastic conditions, they can also form nodules that appear in the interfollicular space or interstitium. C cells can rarely also be found in the colloidal lumen. Such cells could possibly derive their origin from stem endodermal cells and thereby possess an inherent ability to traverse the basement membrane.

References

1. Delellis RA, Nunnemacher G, Wolfe HJ, C cell hyperplasia, an ultrastructural analysis, 1977, march36(3):237-48.
2. Albores Saavedra J.A., Gorraez De La Mora T., De La Torre-Rendon F. et al., Mixed medullary carcinoma of the thyroid. A previously unrecognized variant of thyroid carcinoma, Hum Pathol, 1990, 21:1151–1155.
3. Bussolati G., Pearse A.G.E., Immunofluorescent localization of calcitonin in the C-cells of the pig and dog thyroid, J Clin Endocrinol, 1967, 37:205–209.
4. Carcangui M.L., Thyroid. In: Sternberg, S.S. (ed), Histology for pathologists, 2nd edition, Lippincott-Raven Publishers, Philadelphia, 1997, 1075–1093.
5. Livosi V.A., Surgical pathology of the thyroid, WB Saunders Company, Philadelphia, 1990 1990.
6. Gmünder-Lehner RB, Okamoto E, Hedinger C, Distribution of C cells in the human thyroid gland Schweiz Med Wochenschr., 1983 Oct 1;113(39):1385-94.
7. Apel R, Ezzat S, Bapat BV, Pan N, LiVolsi VA, Asa SL. 1995 Clonality of thyroid nodules in sporadic goiter. Diagn Molec Pathol. 4:113–121.
8. Kracht, J., Hachmeister, U., Christ, U. C cells in the human thyroid in: Proceedings of the Second International Symposium. Calcitonin. Heinemann Medical Books, London; 1969:274–280.
9. Serge Guyétant, Marie-Christine rousselet, Michel Durigon, Daniel Chappard, Brigitte Franc, Olivier Guerin, and Jean-paul saint-andré, Sex-Related C Cell Hyperplasia in the Normal Human Thyroid: A Quantitative Autopsy Study, Journal of Clinical Embryology & Metabolism, 1997, Vol 82 , No 1, pp:42-47.
10. Nunez EA, Gould RP, Hamilton, DW, Hayward, JS, Holt, SJ (1967) Seasonal changes in the fine structure of the basal granular cells of the bat thyroid. J Cell Sci 2: 401-410.
11. Azzali, G. 1968. Ultrastructure of parafollicular cells. In Calcitonin: Symposium on Thyrocalcitonin and C Cells. S. Taylor, editor. Heinemann Ltd., London. 152.
12. Wissing, S. L. 1962. The fine structure of parafollicular (light) cells of the rat thyroid gland. Proc. 5th Int. Congr. Electron Microsc. 2:1.
13. Ekholm, R., and L. E. Ericson. 1968. Ultrastructure of the parafollicular cells of the thyroid gland in the rat. J. Ultrastruct. Res. 23:378.
14. Radivoj V. Krstic, Human microscopic anatomy: An atlas for students of Medicine and biology, corrected 2nd printing 1994, pp278.
15. Lance A. Liott, Adhere, Degrade, and Move: The Three-Step Model of Invasion, Cancer Res; 76(11); 3115-7, June 1, 2016.
16. Harach HR (1997) Histogenesis of thyroid C-cell carcinoma. Curr Top Pathol 91:15–20.
17. Papotti M., Volante M., Komminoth P. et al., Thyroid carcinomas with mixed follicular and C-cell differentiation patterns, Semin Diagn Pathol, 2000, 2:109–119.