Int J Pharm Bio Sci 2013 July; 4(3): (B) 64 - 82

Research Article **Cytology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

THE STUDY OF MAST CELLS IN VARIOUS THYROID DISORDERS

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ABSTRACT

Mast cells are distributed throughout the body, increased proportions are present in the skin, respiratory tract, gastrointestinal tract, uterus and urinary bladder but functions of mast cell in health and disease are not well understood. Mast cell granules store wide variety of mediators of inflammation like heparin, histamine, serotonin, 5-HT, various chemotactic factors, slow reacting substances of anaphylaxis, prostaglandins and various enzymes and their release signals a number of physiological defense responses. The mast cells play a vital role in various inflamatory and immunopathologic reactions often linking the humoral and cell mediated phases of the process. Mast cell alterations have been documented in neoplasms, alteration number of mast cells discharging their granules is observed in goitre and adenomatous thyroid;hence the present study documents the study of relation of mast cells in various thyroid disorders.

KEYWORDS: **Mast cell, thyroid disorders.**

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INTRODUCTION

Mast cell is a secretory alarm cell. Upon the slightest disturbances, they release chemical signals, which diffuse through the surrounding ground substance and trigger the process of inflammation. The functions of mast cell in health and disease are not well understood. Majority of the mast cells are residing in the interface of environment and organism. Mast cell is a connective tissue-resident granulated cell and occurs as small individual cell scattered rather widely throughout the body, particularly in association with blood vessels and nerves. Though, mast cells are distributed throughout the body, increased proportions are present in the skin, respiratory tract, gastrointestinal tract, uterus and urinary bladder(1). Von Reckling Hausen in 1863, discovered the granular cells in unstained mesentry of the frog. Subsequently Ehrlich in 1877 introduced the term for these cells as “Mast Zellen” to characterize cells with numerous metachromatic granules and appeared “stuffed or well fed”. The word “Mast” referring to food and the secretory vesicles of mast cells were interpreted as evidence of ingestion by phagocytosis – suggesting a cell which has eaten its fill of “mast”. Paul Ehrlich was the first person to point out that mast cells are associated with blood vessels, nerves, inflamed tissues and glands. Since Ehrlich’s original description, many theories have been proposed for the origin of mast cells. Currently, it is believed that mast cell originates from the pleuripotent haemopoietic progenitor cell in bone marrow. On structural basis, mast cell can be defined as ‘a connective tissue element which possesses cytoplasmic granules that stain metachromatically under ordinary conditions(2).In light microscopic preparation, mast cell is characterized by largeovoid cell with a round to oval nucleus and cytoplasm densely packed withlarge granules that stain indistinctly with H&E. They are identifiable whenstained with toluidine blue, cresyl voilet, azure-A and methylene blue due topresence of metachromatic granules in the cytoplasm. Mast cell granulesstore wide variety of mediators of inflammation like heparin, histamine, serotonin, 5-HT, various chemotactic factors, slow reacting substances of anaphylaxis, prostaglandins and various enzymes and their release signals a number of physiological defense responses. Paul Ehrlich demonstrated that the granules of mast cells not only display great avidity for basic dyes like toluidine blue but also tend to alter the colour of the dye. This property of metachromasia, or colour change is known to be due to the high content of sulphated mucopolysaccharides, especially heparin(3).

Electron microscopic examination of mast cells reveals numerous large and long villi at their periphery. The granules appear as round, oval or angular shaped membrane bound structures. Recent immunostructural observations indicate that various granules correlate with distribution of serine proteinases, tryptase and chymase within granules. Mast cells can also be projected as tissue cells bearing high affinity binding sites for IgE, synthesizing and storing histamine and proteoglycans within cytoplasmic granules(4). The mast cells play a vital role in various inflamatory and immunopathologic reactions often linking the humoral and cell mediated phases of the process. The cross-linking of high affinity binding sites of mast cells with IgE occurs after exposure to neuropeptides such as substance P; after mechanical or thermal stimuli, which causes degranulation of mast cells. Degranulation of mast cells generally occurs within minutes of exposure to stimuli and usually entire granules are extruded. Concomitant with their release into the extracellular space, the granules release their preformed and stored mediators – Histamine, Heparin, serine proteases and certain cytokines, which may contribute to allergic inflammation and chronic inflammation.The Naphthol AS-D chloroacetate esterase reaction has proved to be very reliable for enzyme-histochemical identification of tissue mast cells(5). Biological capabilities of mast cells include a role in phagocytosis, in innate

immunity, involvement in host defence mechanisms against parasitic infestations, immuno modulation, tissue repair and angiogenesis(6). Mast cells are distributed chiefly in the vicinity of small blood vessels and capsules of various organs(7). Calleja(8) in 1896 has suggested that mast cells are demonstrable throughout the loose connective tissue of man. The term “Mastocytosis” is used to designate the entire class of morbid conditions characterized by abundant proliferation of mast cells. Mast cell distribution has been shown to be altered in various fibroproliferative disorders like pterygium(9); wound healing(10,11); rhinoscleroma(12). Mast cell alterations have been documented in neoplasms like squamous cell carcinoma of the cervix(13), gastric carcinoma(14,15). Prominent increase in mast cells was observed in lesions of breast, like-mammary dysplasia, fibroadenoma and scirrhous carcinoma of breast(16). Inflammation (thyroiditis); benign lesions like follicular adenoma, colloid goitre, nodular goitre and papillary carcinoma of thyroid are the pathologic processes that affect thyroid gland with significant frequency. Many changes have occurred in the field of pathology of thyroid neoplasms since Shields Warren & William A. Meissner wrote two fascicles on thyroid neoplasms. Despite the advancement in fields of diagnosis, surprises never cease. Few studies on thyroid lesions have highlighted that mast cell number are normally present in the stroma and capsule of the thyroid gland(17,18). Increased number of mast cells discharging their granules is observed in goitre and adenomatous thyroid(18,19). Mast cell hyperplasia during goiter formation was studied in 1982(20). Increased number of mast cell observed in sub-acute thyroiditis(21). A careful search of the literature with sources such as Index medicus, Medlar, Medline, Internet etc. reveals the marked paucity of knowledge regarding the variation of mast cells in thyroid lesions. With this stimulus of lacunae in the knowledge of mast cell in various thyroid lesions, an attempt is made to evaluate the mast cell profile in some common thyroid lesions – non-neoplastic and neoplastic.

MATERIALS AND METHODS

The present study was carried out in the Department of Pathology, Mahadevappa Rampure Medical College, Gulbarga. A careful study of thyroidectomy specimens along with relevant clinical data sent for diagnosis in the Department of Pathology, M.R. Medical College, Gulbarga from the Department of General Surgery in Government General Hospital and Basaveshwar Teaching & General Hospital, Gulbarga was done. The study included retrospective and prospective study. The study comprised of common lesions of thyroid, which included:

a) Goitre Colloid Toxic 10 cases each Multinodularity
b) Hashimotos thyroiditis 6 cases
c) Follicular adenoma 10 cases
d) Papillary carcinoma 10 cases
e) Follicular carcinoma 10 cases
f) Medullary carcinoma 6 cases

Mast cell alteration in different neoplasms of thyroid are compared without emphasizing on their variants. Mast cells in control thyroid specimens were counted and compared with the mast cells in various groups. Control samples were chosen from normal thyroid tissues received in thyroidectomy specimens and from cadaveric thyroid specimens.

Diagnostic histomorphological criteria of these conditions are

1. Colloid Goitre

Grossly, the thyroid is symmetrically and diffusely enlarged and may weigh several hundred grams. Histologically, the hyperplastic stage is characterized by epithelial hyperplasia with small follicles, a tall epithelium showing papillary infolding’s, and scanty colloid. In the involution stage, the follicles are large, distended by colloid and lined by flattened cells are the characteristic finding.

2. Multinodular Goitre

Grossly, the thyroid is enlarged and its shape is distorted, one lobe being frequently larger than the other. The thyroid capsule may be stretched

but is intact. On cross-section, multiple nodules are seen, some surrounded by a partial or complete capsule. Secondary changes in the form of hemorrhage, calcification and cystic degeneration are common. Microscopically, there is a wide range of appearance. Some nodule are composed of huge follicles lined by flattened epithelium, others are extremely cellular and hyperplastic and still others are composed predominantly or exclusively by Hurthle cells. Some of the dilated follicles have a conglomerate of small active follicles at one pole (so called Sanderson's polsters).

3. Toxic Goitre

Grossly, the gland shows a mild to moderate symmetric diffuse enlargement. It is succulent and reddish and has the consistency of pancreatic tissue. The cut surface is uniformly gray or red depending on the degree of vascularity. Microscopically, the follicles are markedly hyperplastic with prominent papillary infolding that may cause confusion with papillary carcinoma. The lining epithelium is columnar, with basally located normochromatic or hyperchromatic nuclei and a clear, sometimes microvacuolated cytoplasm. Colloid is pale and finely vacuolated with prominent scalloping where it abuts the epithelium. These above features are not seen in non-toxic goitre.

4. Hashimotos Thyroiditis

Grossly, the thyroid may be three or four times its normal size with firm or rubbery consistency. Cut surface is smooth or vaguely lobulated and uniformly gray or pale yellow and it closely resembles that of a hyperplastic lymph node. Histologically, the two abnormalities are, lymphocytic infiltration of the stroma and oxyphilic change of the follicular epithelium. The lymphoid tissue is distributed within and around the lobules, and it invariably exhibits large follicles with prominent germinal centers. The thyroid follicles are small and atrophic. Most or all of them are lined by variably sized Hurthle cells. The nuclei of these cells may show enlargement and hyperchromasia or conversely, an optically clear appearance and overlapping quality reminiscent of that seen in papillary carcinoma. Connective tissue is scanty, with slight or moderate thickening of the interlobular septa.

5. Follicular Adenoma

Definition: A benign encapsulated tumor showing evidence of follicular cell differentiation. Grossly, adenomas are usually round to oval with diameter between 1- 3 cm and are characteristically surrounded by a complete thin fibrous capsule. Their consistency is rubbery or firm. Cut surface is usually homogenous and without internal lobulation. Colour is usually grayish white to tan depending on the cell composition and amount of colloid present. Histologically, conventional types have been traditionally divided among the following categories.

Trabecular/ Solid

This tumor subtype is very cellular and grows in either a trabecular or diffuse (solid) fashion, with few or no follicles being fgormed. It is sometimes also referred to as embryonal because of its morphologic resemblance to a developing thyroid in a very early (prefollicular) stage.

Microfollicular

In this tumor, neoplastic follicles are formed but are smaller than those of the neighbouring gland. The ratio of cells to lumen is greatly altered in the direction of the formes, and the amount of colloid present is minimal. This subtype is sometimes designated as fetal, following similar embryologic analogies.

Normofollicular (Simple)

The pattern of growth is follicular throughout and the size of the follicles approaches that of the non-neoplastic gland.

Macrofollicular (Colloid)

The neoplastic follicles in this are larger and full of colloid, thus resembling those seen in hyperplastic nodules. The cells of adenomas tend to be polygonal, with normochromatic nuclei that are round to oval. Mitoses are usually absent or scanty. Cytoplasm is

acidophilic to amphophilic and moderately abundant with well defined cell borders. The lumina of the neoplastic follicles contain variable amounts of colloid. The capsule of adenoma is complete and made of fibrous tissue.

6. Papillary Carcinoma

Definition: Papillary carcinoma is a malignant epithelial tumor showing evidence of follicular cell differentiation and characterized by the formation of papillae and/or a set of distinctive nuclear features. The keys to diagnosis are the nuclear characteristics, while demonstration of invasion, either vascular or capsular is not pre-requisite. Grossly, they are typically infiltrative, with irregular, ill defined borders and a hard consistency. They are white to tan, and have a granular texture due to the presence of papillae. The cut surface may be gritty because of presence of psammoma bodies.

Histomorphologically

two features that best characterize typical papillary carcinoma are the papillae and nuclear changes.

1. Papillae: Papillae usually are complex arborizing with delicate fibrovascular cores. However, the papillae can be broad, with the cores being formed by fibrocellular, edematous or hyalinized tissue, which may contain foamy marcophages, adipose cells or small neoplastic follicles. Psammoma bodies, which are laminated calcified structures, are found in approximately half of the cases and are pathognomonic. They occur in the stalks of the papillae, fibrous stroma.

2. Nuclear Features: The nuclei of papillary carcinoma are typically large, crowded, ovoid, ground-glass (Orphan Annie eye) and grooved with small distinct nucleoli. Ground-glass change refers to the emptylooking nuclei with scanty marginated dusty chromatin, believed to be an artifact of formalin fixation because it is usually not evident in frozen sections or cytologic preparations. Another characteristic feature is the nuclear groove formed by deep folding of the nuclear membrane found in almost all cases of papillary carcinoma at least focally. Nuclear psuedo inclusions, which represent intranuclear herniation of pockets of cytoplasm, appear as pale-staining membrane delineated vacuoles are typical of papillary carcinoma. The neoplastic cells are polygonal to cuboidal, but can be flattened, dome shaped, hobnailed or columnar. The cytoplasm is lightly eosinophilic to amphophilic, but can be oxyphilic or clear.

Variants of Pupillary Carcinoma

1. Follicular variant.
2. Solid variant
3. Encapsulated variant
4. Variant with exuberant nodular fascitis like stroma.
5. Diffuse sclerosing variant
6. Diffuse follicular variant
7. Tall cell variant
8. Warthin tumor like variant
9. Macrofollicular
10. Oxyphilic cell variant

Mast cell alteration in different neoplasms of thyroid are compared without emphasizing on their variants.

7. Follicular Carcinoma

Definition: A malignant epithelial tumor showing evidence of follicular cell differentiation and not belonging to any of the other distinctive types of thyroid malignancy. Classification: (on the basis of the degree of invasiveness).

1. Minimally invasive (encapsulated).
2. Widely invasive (Frankly invasive).

Diagnostic Criteria for Follicular Carcinoma

Vascular Invasion: Vascular invasion is a much more reliable sign of malignancy than capsular invasion. To qualify for vascular invasion, the involved blood vessel should be located within the capsule or immediately outside it (rather than within the tumor itself). It should be of large (i.e. venous rather than capillary) caliber and should have an identifiable wall and endothelial lining. The intravascular cells should have a clear cut epithelial appearance and they should project into the vessel lumen in a thrombus like fashion, in such

a way that they partly or completely obliterate it. Most important, they should be attached at some point to the vessel wall.

Capsular Invasion: To qualify for capsular invasion, there must be complete transgression of the fibrous capsule, that is, the tumor bud has to extend beyond an imaginary line drawn through the external countour of capsule. It should be kept in mind that when a follicular carcinoma invades into and through the capsule, it usually does not permeate the surrounding parenchyma, instead, a new fibrous capsule is formed at the leading edge. Vascular invasion and capsular invasion are infact closely related phenomena. Tumors showing vascular invasion almost always show capsular invasion.

8. Medullary Carcinoma

It is a malignant tumor showing parafollicular C-cell differentiation. Grossly, it is often paradoxically circumscribed, although small tumors (less than 7mm) are more often infiltrative. The tumor is firm and grayishwhite tan or reddish brown.

Histologic Appearance

The prototypic histologic appearances of medullary carcinoma are sheets, packets or irregular islands of polygonal or plump spindly cells traversed by delicate fibrovascular septa. Cellular discohesion and interstitial edema are very common. The tumor cell nuclei are round or oval, and typically possess finely stippled chromatin and indistinct nucleoli. The cytoplasm is finely granular.

Variants of medullary thyroid carcinoma

1. Glandular / follicular
2. Oxyphilic
3. Giant cell
4. Clear cell
5. Spindle cell
6. Pigmented
7. Squamous
8. Papillary
9. Small cell

Processing and Staining Technique

The tissues for the histopathological study were fixed in 10% buffered formalin, processed in different strengths of alcohol, cleared in xylene and were embedded in paraffin wax. The sections were cut at 4-5 microns thickness and staining was done with hematoxylin and eosin as routinely and also with 1% aqueous toluidine blue for mast cells. The one stained with hematoxylin and eosin was observed for the confirmation of lesion. Other section stained with 1% toluidine blue was used to study mast cells.

Mast cells staining and counting

To identify the mast cells with typical metachromatic granules, special stain 1% aqueous toulidine blue (at pH 4) was used.

Toluidine blue staining method107

1. Preparation of staining solution: 1 gram of toluidine blue powder is dissolved in 100ml of distilled water and the pH is adjusted to 4. The solution is filtered before use.

2. Staining Procedure: a) The sections were taken on albuminized slides and kept at 60ºC for half an hour. b) The slides were kept in xylene for deparaffinization for 15 minutes. Then, the slides were brought to water in descending grades of alcohol i.e. 100%, 90%, 70%, 50% alcohol and then water wash. The slides were then placed in 1% toluidine blue solution (pH 4) for 1 minute. Then, the slides were rinsed in water, dehydrated in absolute alcohol, cleared in xylene and mounted in DPX.

Results

Mast cell granules – purple.
Background tissue – blue.

Mast Cell Counting and Observation

Toluidine blue stained sections were examined under high power magnification. The number of mast cells present in ten consecutive high power fields were counted in all the sections. Findings were tabulated and were statistically evaluated. On the basis of observations, an attempt was made to study mast cell profile in common lesions of thyroid. A possible

explanation for the significant mast cell alteration if any was attempted.

RESULTS

In the present study, an attempt was made to study the distribution of mast cells in some common thyroid lesions. The study included 10 cases of colloid goitre, 10 cases of multinodular goitre, 10 cases of toxic goitre, 6 cases of Hashimoto's thyroiditis, 10 cases of follicular adenoma, 10 cases of papillary carcinoma, 10 cases of follicular
carcinoma and 6 cases of medullary carcinoma.
The age range (mean) in various conditions was:

- In colloid goitre ..... 18 to 50 years (32.3 years)
- In multinodular goitre ..... 28 to 50 years (35.2 years)
- In toxic goitre ..... 18 to 40 years (29.1 years)
- In Hoshimotos thyroiditis.....20 to 55 years (35.33 years)
- In follicular adenoma..... 22-56 years (36.1 years)
- In papillary carcinoma..... 35-65 years (47.8 years)
- In follicular carcinoma ..... 30-63 years (48.3 years)
- In medullary carcinoma..... 30-59 years (49.5 years) In colloid goitre the M:F ratio was 1:9; in multinodular goitre, the M:F ratio was 1:9, in toxic goitre the M:F ratio was 1:4; in Hoshimotos thyroiditis, all cases were females; in follicular adenoma, the M:F ratio was 3:7; in papillary carcinoma, the M:F ratio was 1:4; in follicular carcinoma, the M:F ratio was 1:9; in medullary carcinoma, the M:F ratio was 1:2. Histologically under H&E staining, classical histological features were observed in each group.In the present study, toluidine blue staining for the demonstration ofmast cell was used as, it is a simple, easy and reliable method to exhibitmetachromatic granules. However, histochemical demonstration of chloroacetate esterase activity in mast cell has been considered as superior method for mast cell identification.

Mast Cell Distribution in Normal Thyroid

On toluidine blue staining, the mast cell distribution in apparently normal thyroid sections ranged between 9 to 15 cells per 10 HPF with a mean of 12.5 cells.

Mast Cell Distribution in Common thyroid Lesions

1. Colloid Goitre

Histopathology: H&E stained sections from colloid goitre cases revealed large follicles distended by colloid and lined by flattened epithelial cells. On toluidine blue staining, the mast cell distribution in colloid goitre cases ranged between 23-29 cells/ 10 HPF, with a mean of 26.8 cells/ 10 HPF. Mast cells were distributed more in the capsular area and less around the thyroid follicles.

2. Multinodular Goitre

Histopathology: H&E stained sections from multinodular goitre cases revealed wide range of appearance, some nodules were composed of huge follicles lined by flattened epithelium. Others were cellular and hyperplastic formed by small follicles with scanty colloid. On toluidine blue staining, the mast cell distribution in multinodular goitre cases ranged between 24-28 cells/ 10 HPF with mean of 26.1 cells. Mast cells were chiefly distributed in capsule and around small blood vessels.

3. Toxic Goitre

Histopathology: H&E stained sections from the cases of toxic goitre revealed medium to large sized follicles lined by a single layer of very flat epithelial cells and pale colloid. At the periphery of the colloid (and in contact with the surface lining epithelial cells) showed numerous vacuoles i.e. scalloping of colloid, indicating resorptive features. On toluidine blue staining, the mast cell distribution in toxic goitre ranged between 20-28 cells 110 HPF with a mean of 24.7 cells. Mast cells
were distributed more in capsule and vascularized stroma.

4. Hashimotos Thyroiditis

Histopathology: H&E stained sections from the cases of Hashimotos thyroiditis revealed lymphocyte infiltration of the stroma with germinal centre formation. The thyroid follicles were small and atrophic. Most of them were lined by Hurthle (oxyphilic) cells with large vesicular nucleus and abundant eosinophilic cytoplasm. On toluidine blue staining, the mast cell distribution in Hashimotos thyroiditis ranged between 24-27 cells/ 10 HPF with a mean of 25.33 cells. Mast cells were distributed more in stroma containing lymphocytic infiltration and were less around the follicles lined by Hurthle cells.

5. Follicular Adenoma

Histopathology: H&E stained sections from follicular adenoma cases revealed follicles of various sizes lined by cuboidal epithelium, and only a few of them filled with colloid. Lesion was completely surrounded by fibrous capsule. On toluidine blue staining, the mast cell count in follicular adenoma cases ranged from 30-39 cells/ 10 HPF with a mean of 36. Mast cells were distributed more in fibrous capsule and in follicular stroma.

6. Papillary Carcinoma

Histopathology: H&E stained sections from papillary carcinoma cases revealed well differentiated papilliferous lesions. Papillae were complex arborizing with delicate fibrovascular core and the surface was covered with a single layer of epithelial cells. Epithelial cells revealed characteristic nuclear features like ground-glass ("Orphan Annie" eye), crowding of nuclei and were grooved with small distinct nucleoli. On toluidine blue staining, the mast cell count in papillary carcinoma cases ranged from 72-80 cells/ 10 HPF with mean of 77.1 cells. Mast cells were distributed more in delicate fibrovascularized papillary core and in capsule.

7. Follicular Carcinoma

Histopathology: H&E stained sections from the cases of follicular carcinoma revealed well-differentiated lesion consisting of follicles of fairly uniform shape and variable size, filled with eosinophilic colloid and lined with a single layer of cuboidal epithelial cells. Lesion demonstrated vascular invasion with tumor plug present within a blood vessel and covered by endothelium. Capsular invasion was seen with tumor bud completely transgressing fibrous capsule i.e. beyond the external contour of the capsule. On toluidine blue staining, the mast cell distribution in follicular carcinoma ranged from 46-50 cells/ 10 HPF with mean of 47.8 cells. Mast cells were distributed more in capsular, sub-capsular fibrous tissue and around blood vessels.

8. Medullary Carcinoma

Histopathology: H&E stained sections from the cases of medullary carcinoma revealed solid sheets and packets of tumors traversed by delicate fibrovascular septa. Lesion showed characteristic abundant amyloid deposits and tumor cell dehiscence. Tumor cells possess regular nuclei with fine chromatin and granular cytoplasm. On toluidine blue staining, the mast cell distribution in medullary carcinoma ranged from 45-48 cells/ 10 HPF with mean of 46.67 cells/ 10 HPF. Mast cells were distributed more around the tumor islands and less near the amyloid deposits.

Table-1
Distribution of Mast Cells in Colloid Goitre Vs Normal Thyroid Mast cells per 10 HPF

	Colloid goitre (CG)	Normal thyroid (N)
Range	23-29	9-15
Average	26.80	12.50

CG Vs N t = 15.89 p <0.001 Highly significant

Table-2
Distribution of Mast Cells in Multinodular Goitre Vs Normal Thyroid Mast cells per 10 HPF

	Multinodular goitre (MNG)	Normal thyroid (N)
Range	24 – 28	9 – 15
Average	26.1	12.5

MNG Vs N t = 16.19 p <0.001 Highly significant

Table-3
Distribution of Mast Cells in Toxic Goitre Vs Normal Thyroid Mast cells per 10 HPF

	Toxic Goitre (TG)	Normal thyroid (N)
Range	20 – 28	9 – 15
Average	24.7	12.5

TG Vs N t = 10.51 p <0.001 Highly significant

Table-4
Distribution of Mast Cells in Hashimoto's Thyroiditis Vs Normal Thyroid Mast cells per 10 HPF

	Hashimoto's thyroiditis (HT)	Normal thyroid (N)
Range	24 – 27	9 – 15
Average	25.33	12.5

HT Vs N t = 13.09 p <0.001 Highly significant

Table-5
Distribution of Mast Cells in Follicular Adenoma Vs Normal Thyroid Mast cells per 10 HPF

	Follicular Adenoma (FA)	Normal thyroid (N)
Range	30 – 39	9 – 15
Average	36.0	12.5

FA Vs N t = 19.58 p <0.001 Highly significant

Table-6
Distribution of Mast Cells in Papillary Carcinoma Vs Normal Thyroid Mast cells per 10 HPF

	Papillary Carcinoma (PC)	Normal thyroid (N)
Range	72 – 80	9 – 15
Average	77.1	12.5

PC Vs N t = 55.68 p <0.001 Highly significant

Table-7
Distribution of Mast Cells in Follicular Carcinoma Vs Normal Thyroid Mast cells per 10 HPF

	Follicular Carcinoma (FC)	Normal thyroid (N)
Range	46 – 50	9 – 15
Average	47.8	12.5

FC Vs N t = 40.11 p <0.001 Highly significant

Table-8
Distribution of Mast Cells in Medullary Carcinoma Vs Normal Thyroid Mast cells per 10 HPF

	Medullary Carcinoma (MC)	Normal thyroid (N)
Range	45 – 48	9 – 15
Average	46.67	12.5

MC Vs N t = 34.17 p <0.001 Highly significant

Table-9
Distribution of Mast Cells in Toxic Goitre Vs Colloid Goitre Mast cells per 10 HPF

	Toxic goitre (TC)	Colloid Goitre (CG)
Range	20 – 28	23 – 29
Average	24.7	26.8

TG Vs CG t = 0.78 p >0.05 Insignificant

Table-10
Distribution of Mast Cells in Toxic Goitre Vs Multinodular Goitre Mast cells per 10 HPF

	Toxic goitre (TC)	Multinodular Goitre (MNG)
Range	20 – 28	24 – 28
Average	24.7	26.1

TG Vs MNG t = 1.32 p >0.05 Insignificant

Table-11
Distribution of Mast Cells in Colloid Goitre Vs Multinodular Goitre Mast cells per 10 HPF

	Colloid goitre (CG)	Multinodular goitre (MNG)
Range	23 – 29	24 – 28
Average	26.8	26.1

CG Vs MNG t = 0.85 p >0.05 Insignificant

Table-12
Distribution of Mast Cells in Hashimoto's Thyroiditis Vs Multinodular Goitre Mast cells per 10 HPF

	Hashimoto's thyroiditis (HT)	Multinodular goitre (MNG)
Range	24 – 27	24 – 28
Average	25.33	26.1

HT Vs MNG t = 1.04 p >0.05 Insignificant

Table-13
Distribution of Mast Cells in Colloid Goitre Vs Hashimoto's Thyroiditis Mast cells per 10 HPF

	Colloid goitre (CG)	Hashimoto's Thyroiditis (HT)
Range	23 – 29	24 – 27
Average	26.8	25.33

CG Vs HT t = 1.55 p >0.05 Insignificant

Table-14
Distribution of Mast Cells in Hashimoto's Thyroiditis Vs Toxic Goitre Mast cells per 10 HPF

	Hashimoto's thyroiditis (HT)	Toxic goitre (TG)
Range	24 – 27	20 – 28
Average	25.33	24.7

HT Vs TG t = 0.48 p >0.05 Insignificant

Table-15
Distribution of Mast Cells in Follicular Adenoma Vs Multinodular Goitre Mast cells per 10 HPF

	Follicular Adenoma (FA)	Multinodular Goitre (MNG)
Range	30 – 39	24 – 28
Average	36.0	26.1

FA Vs MNG t = 8.92 p <0.001 Highly significant

Table-16
Distribution of Mast Cells in Follicular Adenoma Vs Papillary Carcinoma Mast cells per 10 HPF

	Follicular Adenoma (FA)	Papillary Carcinoma (PC)
Range	30 – 39	72 – 80
Average	36.00	77.1

FA Vs PC t = 18.76 p <0.001 Highly significant

Table-17
Distribution of Mast Cells in Follicular Adenoma Vs Follicular Carcinoma Mast cells per 10 HPF

	Follicular Adenoma (FA)	Follicular Carcinoma (FC)
Range	30 – 39	46 – 50
Average	36.00	47.80

FA Vs FC t = 10.35 p <0.001 Highly significant

Table-18
Distribution of Mast Cells in Follicular Adenoma Vs Medullary Carcinoma Mast cells per 10 HPF

	Follicular Adenoma (FA)	Medullary Carcinoma (MC)
Range	30 – 39	45 – 48
Average	36.00	46.67
FA Vs MC	***t = 7.79 p <0.001 Highly significant***	

Table-19
Distribution of Mast Cells in Papillary Carcinoma Vs Follicular Carcinoma Mast cells per 10 HPF

	Papillary Carcinoma (PC)	Follicular Carcinoma (FC)
Range	72 – 80	46 – 50
Average	77.10	47.80
PC Vs FC t = 26.88 p <0.001 Highly significant		

Table-20
Distribution of Mast Cells in Papillary Carcinoma Vs Medullary Carcinoma Mast cells per 10 HPF

	Papillary Carcinoma (PC)	Medullary Carcinoma (MC)
Range	72 – 80	45 – 48
Average	77.10	46.67
PC Vs MC t = 23.41 p <0.001 Highly significant		

Table-21
Distribution of Mast Cells in Follicular Carcinoma Vs Medullary Carcinoma Mast cells per 10 HPF

	Follicular Carcinoma (FC)	Medullary Carcinoma (MC)
Range	46 – 50	45 – 48
Average	47.80	46.67
FC Vs MC t = 1.34 p >0.05 Insignificant		

There was statistically significant increase in the mast cell count in colloid goitre, multinodular goitre, toxic goitre, Hashomoto's thyroiditis, follicular adenoma, papillary carcinoma, follicular carcinoma and medullary carcinoma when compared with those in normal thyroid. Even though the mast cell count was apparently increased in non-toxic goitre as compared to

toxic goitre, it was not statistically significant. Statistically significant increase was noted in mast cell count in follicular adenoma as compared to multinodular goitre. Mast cell count was significantly increased in papillary carcinoma, follicular carcinoma and medullary carcinoma as compared to follicular adenoma. Statistically significant increase was noted in mast cell counts in papillary carcinoma as compared with mast cell counts in follicular carcinoma and medullary carcinoma.

DISCUSSION

Mast cells are phenotypically and functionally versatile effector cells. When activated by IgE dependent or other mechanisms, mast cells produce and release a diverse array of mediators including histamine, heparin, proteases, lipid mediators and cytokines and play vital role in health as well as in various disease states in human beings. One key facet of the mast cell functions is to initiate and orchestrate the acute inflammation that represents an important part of the early host response to microbial infection. The present study of mast cell profile in some common thyroid lesions is a preliminary effort to probe into the mast cell distribution in non-neoplastic thyroid lesions like colloid goitre, multinodular goitre, toxic goitre and Hashimoto's thyroiditis and in thyroid neoplasms like follicular adenoma, papillary carcinoma, follicular carcinoma and medullary carcinoma. Although, the number of cases in the present study is not very large, it appears to be adequate to draw certain logical conclusions. It is to be specially emphasized that after a careful search on Medlar, Medline, Internet and Index Medicus, very few reports were available on mast cells in goitre and adenomatous thyroid lesion and no reports could be fished out regarding mast cell alterations in neoplasm of thyroid-benign and malignant. This study is a sincere attempt to probe the facets of mast cell alterations in these lesions of thyroid. There does seem, to be a unanimity that mast cells are advanced cells with unique growth requirements. They remain differentiated and viable in C-kit ligand (KL), also known as STEM CELL FACTOR (SCF) or steel factor, which is a multipotent cytokine that modulates the growth and differentiation of mast cells as well as hematopoietic progenitors. Although, other cells early in differentiation also respond to this factor, as they mature and differentiate, they down regulate C-kit and depend on lineage specific growth factors. This aspect of mast cell biology may account for their many preserved biological activities of other immune cells including lymphocytes, monocytes and neutrophils. SCF also stimulates directional mast cell motility and its activity is potentiated by addition of IL-3108. Mast cells phagocytose, process antigen, produce cytokines and release vasoactive substances. They exhibit an array of adhesion molecules, immune response receptors and other surface molecules that empower the mast cells with an advanced capability to react to multiple non-specific and specific stimuli(6). Mast cells adhere not only to matrix but to other cells as well. The biological consequences of these interactions include mast cell trafficking, presentation of specific growth factors to mast cell and mast cell activation. Interdigitation of lymphocytes and mast cell membranes has been observed in inflamed tissues. Activated mast cells form heterotypic aggregates with Tlymphocytes. There observations suggest a functional relationship between mast cells and lymphocytes that relates to direct contact between these cells(6,7). The activation of mast cells not only causes the release of preformed granules associated mediators, but initiates the de novo synthesis of lipidderived substances. Of particular importance are the cyclo-oxygenase metabolites of arachidonic acid, because these products possess potent inflammatory activity. The mast cells are particularly well placed to enhance venular permeability at tissue sites by inducing the generation of histamine, PGD2, LTC4, LTB4 and PAF6. Several growth factor cytokines are known to affect the growth and differentiation of mast cells including IL-3, IL-4, IL-9, IL-10, SCF and NGF. Mast cell distribution has been shown to be altered in various fibroproliferative

disorders like wound healing9,11, pterygium8, rhinoscleroma(12). Prominent increase in mast cells was observed in fibroproliferative lesions of breast like mammary dysplasia, fibroadenoma and scirrhous carcinoma of breast(16).

The association of mast cells with the tumors of man has been documented as early as 1879. Research literatures are available regarding the presence of mast cell alterations in various tumors of man(22,23) and in various benign versus malignant neoplasms(24). However, results of some studies fail to document a proper statistical correlation. In the present study, the age range in patients with colloid goitre was 18-50 years (mean being 32.3 years); in multinodular goitre, the age ranged from 20-50 years (mean being 35.2 years); in toxic goitre patients, the age ranged from 18-40 years (mean being 29.1 years); in Hashimoto's thyroiditis patients, the age ranged from 20-55 years (mean being 35.33); in 22-56 years (mean being 36.1). The age ranged from 35-65 years (mean being 47.8 years) in patients with papillary carcinoma; in follicular carcinoma, the age range was 30-63 years (mean being 48.3 years); in medullary carcinoma patients, the age ranged from 30-59 years (mean being 49.5 years). The male:female (M:F ratio in cases of colloid goitre was 1:9 in cases of multinodular goitre; M:F ratio was 1:9; in toxic goitre, M:F ratio was 1:4; in Hashimotos thyroiditis, all were females; in follicular adenoma, M:F ratio was 3:7; in papillary carcinoma, M:F ratio was 1:4; in follicular carcinoma, M:F ratio was 1:9 and in medullary carcinoma, M:F ratio was 1:2. This corroborates the fact that thyroid disorders are eventually seen predominantly in females. In the present study, the mast cell count in normal thyroid ranged from 9 to 15 cells per 10 HPF with mean of 12.5 cells. Cases of colloid goitre in the present study showed mast cell count ranging from 23-29 cells/ 10 HPF, with a mean of 26.8 cells. The mast cell count was significantly increased in colloid goitre ($p<0.001$), when compared with the count of normal thyroid tissue. In cases of multinodular goitre, mast cell count ranged from 24-28 cells/ 10 HPF, with a mean of 26.1 cells. The mast cell count was significantly increased in multinodular goitre ($p<0.001$) when compared with the count in normal thyroid tissue. The mast cell density was more in capsular and follicular stromal connective tissue. In cases of toxic goitre, mast cell count ranged from 20-28 cells per 10 HPF, with mean of 24.7 cells. The mast cell count was significantly increased in toxic goitre when compared with count of normal thyroid tissue. In case of follicular adenoma, mast cell count ranged from 30-39 cells/ 10 HPF (mean being 36 cells). The mast cell count was significantly increased in follicular adenoma cases ($p<0.001$) when compared with normal thyroid tissue. The present observation is similar to that of Blomquist(18) who showed that, mast cell number is increased in goitrous and adenomatous glands of thyroid. Study done by Ziliotto & Pellegrini (19) documented that there is increase in the number of mast cells discharging their granules in goitre, and adenomatous thyroid. The possible explanation regarding increased number of mast cells in these goitrous conditions might be related to the chemical mediators like stem cell factor and cytokines like the various interleukins release. On comparison of mast cell distribution in cases of colloid goitre versus multinodular goitre cases; in toxic versus nodular goitre cases; in toxic goitre versus multinodular goitre cases and colloid goitre versus toxic goitre cases, no statistical significant difference ($p>0.05$) was seen in either of the studies showing statistically insignificant difference between toxic goitre versus nontoxic goitre cases. The comparison of mast cell distribution in cases of multinodular goitre versus follicular adenoma cases showed significant difference ($p<0.001$) with increased count in follicular adenoma cases. This significantly more mast cell in follicular adenoma compared to multi-nodular goitre can be explained on the basis of chemical mediators like Stem Cell Factor (SCF) and interleukins (IL3) which are mast cell chemoattractant and causes mast cell proliferation and differentiation are produced by tumor cells themselves(25). The literature on the mast cell distribution in cases of colloid goitre, multinodular goitre, toxic goitre and follicular adenoma is very scant, as

assorted from Medlar, Medline, Index Medicus and Internet. This study (perhaps the first) emphasizes a systematic documentation of mast cell changes in these thyroid lesions. In Hashimoto's thyroiditis, the mast cell count ranged from 24-27 cells/ 10 HPF with a mean of 25.33 cells. The mast cell count was significantly increased in Hashimotos thyroiditis ($p<0.001$) when compared with the count of normal thyroid. Mast cell density in Hashimoto's thyroiditis was more in the stroma containing lymphocytic infiltrates.

Ekman and Naumann(26) have shown that thyrotrophic hormone (TTH) causes increase in mast cells in human and guinea pig thyroid gland. Asboe-Hansen(27) has stated that thyroxin decreases numerous mast cells of myxedematous skin in man. Cohen et al suggest that lymphocytes may regulate mast cells by the production of specific lymphokines and interleukins. IL3 and IL4 derived from activated T-cells act as growth factor for mast cells and thus expansion of the mast cell population. According to Banovac K(28) , increased mast cells in auto-immune (Hashimotos) thyroiditis possess proteolytic enzymes capable of digesting different host proteins which may have a role in the thyroid cell interaction with the surrounding matrix. Study done by Toda S(21) et al showed, increased numbers of mast cells localize at the lesions of subacute thyroiditis where thyroid tissue is regenerated and also stated that, mast cells play crucial roles in the repair process of the thyroid tissue of the disease via production of various growth factors or biomolecules, modulating thyroid folliculogenesis and angiogenesis. These above all findings supplement the observations of increased mast cells in Hashimotos (autoimmune) thyroiditis. The predominance of mast cells in stroma containing lymphocytic infiltrates of Hashimotos thyroiditis supports the theory that the origin of mast cells is related to the lymphoid cell (especially T-cell)-system(29). On comparison of mast cell distribution in cases of Hashimotos thyroiditis versus colloid goitre cases; in multinodular goitre versus Hashimotos thyroiditis cases and toxic goitre versus Hashimotos thyroiditis cases, no statistical significant difference ($p>0.05$) was seen in either of the studies. The mast cell count in thyroid neoplasms i.e. in follicular adenoma cases ranged from 30-39 cells/ 10 HPF (mean being 36 cells). The mast cell count was significantly increased in follicular adenoma cases ($p<0.001$) when compared with normal thyroid tissue. In cases of papillary carcinoma of thyroid, the mast cell count ranged from 72-80 cells/ 10 HPF (mean being 77.1 cells). The mast cell count was significantly increased in papillary carcinoma cases ($p<0.001$) when compared with normal thyroid tissue. Mast cell density was more in papillary fibrovascular core. In follicular carcinoma cases, the mast cell count ranged from 46-50 cells/ 10 HPF (mean being 47.8 cells). The mast cell count was significantly increased in follicular carcinoma cases ($p<0.001$) when compared with normal thyroid tissue. Mast cell density was more in capsular connective tissue. Abundant stem cell factor produced by the tumor cells may account for the increased number of stromal mast cells, which induce fibroplasia of the surrounding stroma(30). Studies by Folkman and Colleagues suggested that tumor cells themselves secrete an angiogenic factor. This factor belongs to the family of heparin binding growth factors that are ubiquitous in tissues. Roche WR110 suggested that, increased mast cell number liberates, heparin from the granules, which bind to the heparin binding growth factor, angiogenic factor secreted by tumor cells themselves or from other source and causes endothelial migration, proliferation and capillary tube formation and results in neovascularization. Gruber BL(31) et al has found that, the angiogenic factors known to act on endothelial cells and stimulates neovascularization, may simultaneously serve to recruit mast cells to these sites and may explain the intriguing association of mast cells with newly forming blood vessels. In cases of medullary carcinoma of thyroid, the mast cell count ranged from 45-48 cells/ 10 HPF (mean being 46.67 cells).

The mast cell count was significantly increased in medullary carcinoma ($p<0.001$)

when compared with the count in normal thyroid tissue. The mast cell density was more around the tumor cell islands as compared to amyloid deposits. Degranulation of mast cells was seen both in the tumor itself and in the adjacent amyloid deposits. Rukavina(32) et al suggested the role of mast cells in the production of amyloid. Possible explanation regarding decreased mast cells around amyloid deposits might be related to degranulation of mast cells releasing mast-cell specific serine protease, chymase and tryptase. Flynn EA et al has also shown, sequential mast cell migration towards the carcinoma and degranulation during experimental carcinogenesis. Functional significance of phenomenon of accumulation of mast cells around the tumor island was explained by Dimitriadou V(33) et al , suggesting two hypothesis – First one refers to the possibility that the accumulation of mast cells is part of a general immunological host defense reaction since, mast cells have been shown to be cytotoxic for some tumors (especially those sensitive to tumor necrosis factor-alpha). Second possibility suggests, mast cell products could promote tumoral growth and metastasis. In fact, it is well documented that heparin, combined to a range of heparin-binding factors such as bFGF or TGF beta is able to promote neovascularization, and that mast cell proteases cause cell structural alterations and loss of the extracellular matrix integrity and may account for tumor progression and poor prognosis. Mast cell by virtue of secretion of heparin and other chemical mediators can cause vasodilatation, increased vascular permeability, and edema with protein rich exudate. Perhaps such a milieu would favour tumor invasion and tumor spread. Considering all these facts mast cell appears to be an effect rather than a cause in the patho-biology of tumors. On comparison of mast cell distribution in cases of papillary carcinoma versus medullary carcinoma cases; in papillary carcinoma versus follicular carcinoma cases, significant statistical difference ($p<0.001$) was seen in either cases with increased count in papillary carcinoma cases. On comparison of mast cell distribution in cases of follicular carcinoma versus medullary carcinoma cases, no significant statistical difference ($p>0.05$) was seen. Deng JS(34) postulated that T-cells and mast cells are the primary immune cell populations responding to basal cell carcinomas. Inverse relationship was observed between the number of T-cells and mast cells in these tumors and decreased number of T-cells were associated with more aggressive tumors. Same possible explanation may be applied regarding increased number of mast cells in papillary carcinoma of the thyroid when compared to follicular carcinoma and medullary carcinoma of thyroid. Statistically significant difference was noted when mast cell distribution in cases of follicular adenoma was compared versus that in follicular carcinoma ($p<0.001$), papillary carcinoma ($p<0.001$) and medullary carcinoma ($p<0.001$) with increased mast cell in follicular carcinoma, papillary carcinoma and medullary carcinoma. Since there are no documented reports in the medical literature on the mast cell alterations in common benign and malignant neoplasms of thyroid, the present study is perhaps the first to document such alterations. The possible explanation regarding increased number of mast cells in malignant neoplasms (follicular carcinoma, papillary carcinoma and medullary carcinoma) of thyroid may be that the increased release of chemical mediators like stem cell factors and cytokines like various interleukins by tumor cells which cause mast cell migration and proliferation at these sites. In this context, increased mast cells in malignant thyroid lesions may provide an additional/ a supportive parameter in the differentiation between benign versus malignant lesions of thyroid. This study is a sincere attempt to probe the facets of mast cell alterations in common thyroid lesions. A careful review/ search of literature on mast cells in common thyroid lesions has documented the paucity of references. The present study of mast cell profile in common thyroid lesions highlights that:

1. Mast cells can be documented in the thyroid tissue.
2. Mast cell alterations do occur in the common neoplastic and nonneoplastic lesions of thyroid.

3. Mast cell count in non-neoplastic lesions of thyroid (multinodular, colloid, toxic goitre and Hashimotos thyroiditis) was significantly increased as compared to normal thyroid.
4. Mast cell count in neoplastic lesions of thyroid was significantly increased as compared to normal thyroid.
5. Mast cell count was significantly increased in follicular adenomas compared to multinodular goitre.
6. Mast cell count was significantly increased in malignant lesions of thyroid as compared to benign follicular adenoma of thyroid.
7. Mast was increased in papillary carcinomas as compared to follicular carcinoma and medullary carcinoma.
8. Mast cell profile may be an additional diagnostic/ a supportive parameter in the differentiation between benign versus malignant lesions of thyroid.
9. Possible explanatory mechanisms for the above alterations have been suggested. The present study documents striking mast cell alterations in some common non-neoplastic and neoplastic thyroid lesions. Since there are no available reports in the medical literature on these features, the present study is perhaps the first to document such observations.

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