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CLINICOPATHOLOGIAL AND HITOMORPHOMETRIC EVALUATION OF THYROIDECTOMY SPECIMENS IN MULTINODULAR GOITER

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Abstract

Background: Multinodular goiter (MNG) is defined by an architectural remodeling that is heterogeneous; however quantitative comparison with normal thyroid parenchyma is still limited. The system approach of normal versus disease histomorphometry is necessary to properly define pathological deviations. ***Objective:*** To compare the clinicopathological and histomorphometric features of MNG specimens of the thyroid gland with histologically normal tissue in the same thyroids, keeping anatomical and pathological correlates in mind. ***Materials and Methods:*** 80 thyroidectomy specimens (diagnosed as MNG) were compared with 30 control specimens of histologically normal thyroid tissue (from adjacent non-nodular parenchyma confirmed microscopically normal and/or from archival non-pathological thyroid tissue). Clinical information, gross anatomy and microscopic features were documented. The following parameters were measured by digital histomorphometry: follicular diameter, follicular epithelial thickness, and the area percentage of colloid and the stromal proportion. The collected data were analysed using SPSS version 25 software, and Independent t-tests and correlation analysis were performed ($p<0.05$ significant). ***Results:*** There were more females (83.7%) than males, with a mean age of 42.6±11.4 years and most were euthyroid (72.5%). Macroscopically, the MNG specimens had multinodularity, cystic changes, haemorrhage and fibrosis. The histological features of MNG were follicular size variability, colloid accumulation, epithelial hyperplasia, and stromal expansion. Compared to normal tissue, MNG nodules demonstrated significantly larger follicular diameter in colloid-rich areas (286.4±48.2 vs 138.6±21.4 µm, $p<0.001$), increased epithelial height in hyperplastic zones (8.7±1.9 vs 4.3±0.7 µm, $p<0.001$), elevated colloid proportion (61.5±10.4 vs 36.8±8.9%, $p<0.001$), and expanded stromal area (24.3±6.7 vs 11.2±3.4%, $p<0.001$). In 5% of MNG cases incidental papillary thyroid carcinoma was found. Anatomical nodularity was associated with foci of hyperplasia and involution, while the normal tissue had a uniform lobular-follicular architecture. ***Conclusion:*** The quantitative comparison showed that there is a high deviation in the architectural and morphometric features of MNG compared to the normal thyroid. Association of histomorphometry with clinicopathological and anatomical evaluation provides a better diagnostic precision, helps understand the remodeling of the tissues and helps differentiate between benign hyperplastic cycles and early stages of neoplastic transformation that drives these changes.

Keywords: Thyroidectomy; Multinodular goiter; Clinicopathological correlation; Normal vs diseased thyroid; Thyroid follicular architecture; Histomorphometry.

INTRODUCTION

Multinodular goiter (MNG) is one of the most commonly seen thyroid gland disorders and is a leading cause of thyroid enlargement in the world, especially in iodine deficient areas.(1) It is defined as irregular nodular changes in thyroid parenchyma as a result of multiple hyperplastic, involutional, hemorrhagic and fibrotic cycles.(2) Although most patients with multinodular goiter are asymptomatic, the progressive growth of the gland can cause cosmetic deformity, compression symptoms, dysphagia, dyspnea and thyroid function changes.(3) Thyroidectomy is performed to treat surgical disease usually in patients with palpable or suspicious thyroid nodules and cosmetically disturbing thyroid enlargement. (4)

In multinodular goiter, a wide range of histopathological changes occur in the thyroid gland. On gross examination, the gland is usually nodular and has areas of cystic degeneration, calcification, and hemorrhage and areas of fibrosis. (5) On the microscopic level, the lesions can show hyperplastic follicles, colloid rich follicles, papillary infoldings, stromal fibrosis, chronic inflammatory infiltrates and degenerative changes.(6) The significance of these morphological variations lies in the fact that they can simulate or be found with neoplastic processes such as papillary thyroid cancer and follicular tumors. (7) Thus, careful histopathological examination of thyroidectomy specimens is of great importance to differentiate the benign proliferative changes from the malignant transformation. (8)

Histomorphometry is an important tool for the histopathological evaluation that is an adjunct because it gives a quantitative measurement of tissue architecture.(9) Histomorphometric analysis is an objective measurement in thyroid pathology that can be used to assess follicular diameter, epithelial height, the proportion of colloid, nuclear characteristics and stromal components. (10) This quantitative parameter is useful in the understanding of the structural changes of multinodular goiter and could be helpful in differentiating reactive, hyperplastic and neoplastic lesions. (11)

Histomorphometric studies can also be used to gain insight into the biological behaviour of thyroid tissue and its adaptive response to hormonal and environmental factors. From a clinical standpoint, a multinodular goiter shows a great clinical diversity in age, sex distribution, duration of the disease and thyroid functional status. (12) Women are more often affected than men, perhaps because hormone and autoimmune factors affect thyroid function. The clinical picture may be euthyroid, hypothyroid or hyperthyroid, and the heterogeneity of the disease is further illustrated. Therefore, it is essential to have correlation between the clinical findings and microscopic morphology to enable thorough evaluation of the disease. (13)

Although multinodular goiter is a very common condition, there is a lack of integrated data relating clinicopathological characteristics with detailed histomorphometric analysis of thyroidectomy specimens. Most studies are presented with regard to clinical results or routine histopathological diagnosis without quantitative microscopic analysis. Combined clinicopathological and histomorphometric approach could contribute in better understanding of disease progression and tissue remodeling and associated pathological changes.

MATERIALS AND METHODS

Study Design & Setting: Comparative Cross sectional study for 1 year in Department of Histopathology in collaboration with General Surgery at Nishter medical university Multan. Pakistan. The Institutional Review Board (IRB) has approved this study.

Study Population: The cases were collected as a case group of 80 consecutive cases of thyroidectomy specimens from patients clinically and radiologically diagnosed with MNG. Exclusion: children and adolescents with thyroid disorders, other patients with thyroid surgery. Exclusion: any known malignancy, recurrent lesions, autolyzed/poorly fixed tissue. Control Group: 30 specimens of normal thyroid tissue, histologically. The specimens were collected from: (1) adjacent non-nodular parenchyma in MNG specimens, which were microscopically normal (no hyperplasia, fibrosis, inflammation or architectural distortion); and (2) archival thyroid tissue from non-thyroid neck surgery with incidental normal thyroid sampling. Where possible, age and sex matched controls were used.

Data Collection: Medical records were used to extract clinical data, including clinical demographics, duration of symptoms, compressive features and thyroid function tests. Gross & Microscopic Examination: The specimens were fixed in 10% neutral buffered formalin for 24-48 hours. Gross parameters were weight, size, nodularity, cystic/hemorrhagic/calcific changes, and capsular integrity. Representative samples of the nodular areas, adjacent non-nodular parenchyma, and suspicious areas were processed, paraffin embedded, sectioned at 4–5 µm, and stained with H&E. Microscopic examination evaluated the follicular architecture, the colloid content, epithelial morphology, stromal composition, hemorrhage, calcification, cystic change, and inflammatory infiltrates. Normal control tissue was examined for uniformity in size of the follicles, single layer cuboidal epithelium, moderate homogeneous colloid, and minimal interfollicular stroma.

Histomorphometric Analysis: Digital imaging system attached to light microscope was used. Each of 10 randomly selected high-power fields was measured with ImageJ software. The measurements taken: Follicular diameter (µm), Follicular epithelial Height (µm), Follicular colloid area percentage (%), and Follicular stromal area percentage (%). Measurements were taken for each specimen and mean values calculated. Data Analysis: SPSS v25 software was used for statistical analysis. Data from continuous variables were reported as mean± standard deviation (SD). Independent t-test was used to compare parameters of the MNG with those of normal tissue. The one-way ANOVA was used to conduct comparisons of the subgroups within MNG (colloid-rich vs hyperplastic vs fibrotic). Pearson/Spearman tests were used to evaluate the correlation between clinical and morphometric parameters; $p<0.05$ was considered statistically significant. RESULTS Demographics & Clinical Features: There were 67 females (83.7%) and 13 males (16.3%), with a mean age of

42.6±11.4 years. Swelling of the neck was the most common (100%) followed by dysphagia (23.8%) and dyspnea (13.7%). Thyroid status: euthyroid (72.5%), hypothyroid (17.5%), hyperthyroid (10.0%). There were no thyroid abnormalities in the controls. Multinodularity was seen in all the MNG specimens studied in gross anatomy. Cystic degeneration (57.5%), hemorrhage (38.7%), fibrosis (33.8%), and calcification (22.5%) were frequent. Colloid-rich nodules constituted 65%. Normal controls showed smooth, even external surfaces with no nodularity, cysts, hemorrhage or calcification.

RESULTS

A total of 80 thyroidectomy specimens diagnosed as multinodular goiter were evaluated during the study period. The age of the patients ranged from 21 to 68 years, with a mean age of 42.6± 11.4 years. The highest frequency of cases was observed in the 31–40 years age group. Female patients constituted the majority of cases with a female-to-male ratio of approximately 5:1. Most patients presented with gradually enlarging anterior neck swelling, while pressure symptoms such as dysphagia and dyspnea were observed in a smaller proportion of cases. The majority of patients were euthyroid at the time of surgery, whereas hypothyroidism and hyperthyroidism were less frequently encountered.

Table 1: Demographic and Clinical Characteristics of Patients

Variable	Frequency (n=80)	Percentage (%)
Age Group (Years)		
21–30	14	17.5
31–40	28	35.0
41–50	21	26.3
51–60	12	15.0
>60	5	6.2
Gender		
Male	13	16.3
Female	67	83.7
Presenting Symptoms		
Neck swelling	80	100
Dysphagia	19	23.8
Dyspnea	11	13.7
Pain	8	10.0
Thyroid Functional Status		
Euthyroid	58	72.5
Hypothyroid	14	17.5
Hyperthyroid	8	10.0

Gross examination of thyroidectomy specimens revealed multinodularity in all cases. Cystic degeneration was the most common gross finding followed by hemorrhage and calcification. The nodules varied considerably in size and appearance.

Table 2: Gross Pathological Findings in Thyroidectomy Specimens

Multinodularity	80	100
Cystic degeneration	46	57.5
Hemorrhage	31	38.7
Calcification	18	22.5
Fibrosis	27	33.8
Colloid-rich nodules	52	65.0

Microscopic examination demonstrated variable-sized thyroid follicles with abundant colloid accumulation in most cases. Follicular epithelial hyperplasia and stromal fibrosis were frequently observed. Areas of hemorrhage, hemosiderin-laden macrophages and chronic inflammatory infiltrates were also noted in several specimens. Incidental papillary thyroid carcinoma was identified in a small number of cases.

Table 3: Histopathological Findings in Multinodular Goiter

Histopathological Feature	Frequency (n=80)	Percentage (%)
Variable-sized follicles	80	100

Colloid accumulation	63	78.8
Follicular hyperplasia	48	60.0
Stromal fibrosis	36	45.0
Chronic inflammation	22	27.5
Hemorrhage	29	36.3
Calcification	16	20.0
Cystic change	41	51.3
Incidental papillary carcinoma	4	5.0

Histomorphometric analysis revealed significant variation in follicular diameter and epithelial height among the examined specimens. Increased follicular diameter was associated with abundant colloid accumulation, whereas increased epithelial cell height was more prominent in hyperplastic areas.

Table 4: Histomorphometric Parameters of Thyroidectomy Specimens

Histomorphometric Parameter	Mean± SD
Follicular diameter (µm)	286.4± 48.2
Follicular epithelial height (µm)	8.7± 1.9
Colloid area percentage (%)	61.5± 10.4
Stromal area percentage (%)	24.3± 6.7

Histomorphometric parameters were compared between the 80 MNG specimens and 30 histologically normal thyroid tissue controls using independent t-tests. All measured parameters showed statistically significant differences between the two groups (Table 5).

Table 5: Comparative Histomorphometric Parameters: Multinodular Goiter vs. Normal Thyroid Tissue

Parameter	MNG (n=80) Mean±SD	Normal Control (n=30) Mean±SD	Mean Difference	p-value
Follicular diameter (µm)	286.4± 48.2	138.6± 21.4	+147.8	<0.001
Follicular epithelial height (µm)	8.7± 1.9	4.3± 0.7	+4.4	<0.001
Colloid area percentage (%)	61.5± 10.4	36.8± 8.9	+24.7	<0.001
Stromal area percentage (%)	24.3± 6.7	11.2± 3.4	+13.1	<0.001

Independent t-test; $p<0.05$ considered statistically significant

- **Follicular diameter** in MNG specimens was more than double that of normal thyroid tissue (286.4±48.2 µm vs. 138.6±21.4 µm, $p<0.001$), reflecting marked follicular dilatation associated with colloid accumulation and involutional changes.
- **Epithelial height** was significantly increased in MNG compared to controls (8.7±1.9 µm vs. 4.3±0.7 µm, $p<0.001$), consistent with epithelial hyperplasia in active nodular areas.
- **Colloid area proportion** was substantially higher in MNG (61.5±10.4% vs. 36.8±8.9%, $p<0.001$), supporting the predominance of colloid-rich, inactive follicles in multinodular goiter.
- **Stromal area percentage** was significantly expanded in MNG specimens (24.3±6.7% vs. 11.2±3.4%, $p<0.001$), corresponding to the fibrotic and inflammatory stromal remodeling observed microscopically.

When MNG specimens were stratified by predominant histological pattern:

- Colloid-rich nodules (n=52) exhibited the largest follicular diameters (312.5±39.1 µm) but relatively lower epithelial height (6.9±1.2 µm).
- Hyperplastic-predominant nodules (n=48) showed increased epithelial height (10.8±1.4 µm) with moderate colloid proportion (48.3±9.2%).
- Fibrotic nodules (n=27) demonstrated the highest stromal area percentage (35.6±5.8%, $p<0.001$ vs. other subgroups).

DISCUSSION

Multinodular goiter is one of the most frequently seen thyroid conditions in the surgical pathologist's office and is a significant health problem in developing countries. The disease is associated with multiple cycles of follicular hypertrophy and regression resulting in architectural and structural variations in the thyroid. The present study revealed that thyroidectomy specimens showed significant morphological variability and some characteristic changes of the thyroid gland associated with multinodular goiter, which was confirmed by the clinicopathological and histomorphometric evaluation.

Most of the patients in the present study were female with over 4/5 of them. The same sex-differences (females outnumbering males) have been reported repeatedly in past studies and might be due to hormonal differences and autoimmunity or variations in iodine metabolism in females. Hegedüs also reported that multinodular goiter was more prevalent in middle-aged females in their 3rd– 5th decades of life. The mean age in this study was similar to those reported in previous regional and international studies, which was evidence that multinodular goiter is mostly a disease of the adult population, and progresses slowly over a period of years. (14)

In this study, the most frequent clinical manifestation was neck swelling, that is, a universal symptom, and compressive symptoms, like dysphagia and dyspnea, were observed less frequently. In similar observations, Prades et al. mentioned that pressure symptoms are usually present in the large, long-standing goiters with multiple nodules. (15) In the present study, the majority had euthyroid states while a few had hypo- or hyperthyroid states. This conclusion is consistent with previous studies which showed that functional status in patients with multinodular goiter may be dependent on the presence or absence of follicular activity and hormonal imbalance. In the present case, gross pathological examination of all the specimens showed the presence of multi-nodularity, with the presence of cystic degeneration, fibrosis, haemorrhage, and calcification. These changes are indicative of chronic degenerative changes within hyperplastic tissue of the thyroid.

Chavez et al, explained analogous gross changes in multinodular goiter, noting that nodular changes and degenerative changes are the result of multiple cycles of hyperplasia and involution. Inactive or involuted follicles containing a large amount of colloid material were among the most frequent features found in this study, and were considered to be 'colloid-rich nodules'. (16) Microscopically, a histological pattern of variable sized follicles with flattened to cuboidal epithelium and abundant accumulation of colloid was the predominant pattern. These were commonly seen along with follicular hyperplasia, stromal fibrosis and cystic degeneration. These findings are consistent with the pathological process of multinodular goiter, in which the thyroid is alternately stimulated by TSH, causing hyperplastic and involutional phases.

One of the key findings of this study was that incidental papillary thyroid cancer was detected in a minority of cases. A few studies have reported the presence of an occult malignancy in thyroidectomy specimens with a presumed diagnosis of MNG. Frates et al. reported that multinodular goiter does not rule out the presence of carcinoma and that careful histopathological sampling should be performed. (17) Careful microscopic examination in thyroidectomy specimens is highlighted by the presence of incidental malignancy. Objective evaluation of the microscopic architectural alteration was a crucial part of the present study, which was carried out by histomorphometric analysis.

Follicular diameter increased mainly in the colloid-rich areas, but increased epithelial cell height was related to hyperplastic areas. These results suggest different functional activities of the thyroid gland. Histomorphometric evaluation has been demonstrated to minimize the inter-observer variability in interpretation of the microscope and to facilitate a quantitative estimation of changes within the tissues. The morphometric parameters like epithelial height and follicular diameter have been shown to be indicative of functional status and proliferative activity of thyroid follicles in studies by Emre et al. In this study the stromal area percentage was correlated with the level of fibrosis and chronic inflammatory infiltration seen on microscopy. (18)

In a sub-set of specimen, chronic inflammation was noted indicating possible autoimmune or inflammatory processes. The coexistence of chronic thyroiditis and multinodular goiter has also been reported in previous studies and could lead to architectural distortion and thyroid dysfunction. In general, the results in this study revealed that multinodular goiter has multiparametric clinicopathological and histomorphometric features. Applying quantitative histological assessment in addition to routine histopathology, allows measurable parameters related to follicular activity and tissue remodeling. A combined clinicopathological and histomorphometric examination, therefore, helps in better understanding of the disease morphology, and can be helpful in detecting any associated pathological lesions, such as the possible presence of occult malignancy.

CONCLUSION

The morphological changes in goiter formation known as multinodular goiter are characterized by several significant deviations from normal thyroid tissue, including the enlargement of the thyroid glands, the thickening of the thyroid glands and the infiltration of the thyroid glands. Comparative clinicopathological and histomorphometric approach offers objective quantification of disease-induced tissue remodeling, improve diagnostic accuracy, and increase the likelihood of detecting occult malignancies. Thyroid baseline comparison should become routine in thyroid pathology for better clinical decision making and surgery. The quantitative comparison confirmed that MNG exhibits significant architectural deviation from normal thyroid parenchyma, with follicular dilatation, epithelial hyperplasia, colloid accumulation, and stromal expansion being the hallmark morphometric alterations.

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