International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2021; 4(3): 110-115
Received: 01-07-2021
Accepted: 02-08-2021

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A study of cytological and histopathological correlation in nodular goiter and its associated lesions with emphasis on morphological patterns and Epidemiology

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DOI: https://doi.org/10.33545/pathol.2021.v4.i3b.400

Abstract
Background: To evaluate the different patterns of thyroid lesions associated with MNG in surgically resected specimens and biopsies received at department of pathology and correlate the various histological and cytological diagnosis to ensure the usefulness of cytology prior histopathology.
Methods: The study period is from 2017 to 2020 January carried out in Department of Pathology, GVPIHC&MT on the thyroidectomy specimens for detailed analysis. Prior cytology and histomorphological diagnosis was recorded and analysed.
Results: Various morphological patterns were noted; most common were calcification (85%), cystic change (80%) and Sanderson polsters (75%). 19 nonneoplastic lesions associated with MNG were noted in this study. Most common lesion noted was Hashimoto's thyroiditis constituting 19 cases seen in the age group of 41-60 yrs. 15 benign lesions associated with nodular goiter were noted in this study. 22 malignant lesions were observed to be associated with nodular goiter with most common malignant lesion being papillary thyroid carcinoma followed by its variant papillary micro-carcinoma. The malignant lesions had lymphnodal enlargement with metastases in 9 cases constituting 7 cases of N1a and 2 cases of N1b.TBSRTC Category – I included 10 cases with inadequate smears for reporting. Most of them i.e. 81 cases constituting 63.28% were benign and were included under Category II. Only 7 cases were indeterminate lesions. Category IV included the next highest reported cases after Category II including 17 cases constituting 13.28%. Only 3 cases were included under suspicious category/category V. 7.8% i.e. 10 cases were reported to be malignant.
Conclusions: Taking into consideration histopathology report as a gold standard, correlation of cytological finding with histopathology finding showed 90% sensitivity, 98.8% specificity with 90% positive predictive value.

Keywords: malignant, thyroid, nodular goiter, specificity, histopathology, cytology

Introduction
Thyroid lesions are fairly common worldwide and are commonly encountered in clinical practice [1]. Thyroid lesions may be developmental, inflammatory, hyperplastic and neoplastic. Diseases of the thyroid gland are common and comprise a spectrum of entities causing systemic disease (Grave's disease) or a localised abnormality in the thyroid gland such as nodular enlargement (goitre) or a tumour mass. Thyroid carcinoma closely resembles its benign counterpart in physical characteristics, measurable physiological parameters such as serum T3/T4 levels and ultrasonic characteristics. Therefore, the surgical excision of the nodule and its histological examination is the only way to differentiate between the more frequent benign and much less frequent malignant nodules. A solitary thyroid nodule is defined as a palpable single, clinically detected nodule in the thyroid. It causes more concern because of high probability of malignancy in it, which can range from 5-35% of all solitary thyroid nodules [2]. Diffuse thyroid lesions are those that are associated with conditions affecting entire gland such as hyperplasia and thyroiditis. Nodular lesion comprises those disorders that produce a clinical nodule and consists of non-neoplastic hyperplasia as well as benign and malignant tumours [3]. Neoplasms of the thyroid are relatively uncommon disease. They constitute only 0.7% of all cancers in female and 0.2% in males. There are different diagnostic modalities used to evaluate and diagnose efficiently thyroid nodules.

These include clinical examination, thyroid function test (TFT), Scintiscan, ultrasonography (USG), fine needle aspiration cytology (FNAC) and histopathological examination. However clinical assessment, TFT and USG have been poor parameters for assessing thyroid nodules. Final diagnosis requires morphological examination of lesions and for this FNAC or histological examination becomes mandatory. FNAC is an established technique for the investigation of thyroid lesions. Despite many advantages, FNAC has certain limitations which include specimen adequacy and cytological interpretation, as the sampling is variable and not always representative. Thus a specific diagnosis can only be arrived at after a histological examination.

Materials and Methods

This is a hospital based observational study of various lesions associated with nodular goitre by using FNAC - cytology and finally by histopathology.

The patients were referred by Surgery, General Medicine, ENT, Surgical & Medical Oncology, TB and Chest to our hospital. The duration of study period was from Jan 2017 to Jan 2020. This material included 180 histopathology specimens.

The specimens received were fixed in 10% buffered formalin. After fixation, tissues were processed in graded alcohols, xylol and embedded in paraffin. Routine haematoxylin & eosin staining was applied to sections of paraffin blocks and studied under light microscopy for the confirmation of nodular goiter and associated other thyroid lesions.

All the slides were thoroughly evaluated for histological features and the lesions were categorized into nonneoplastic and neoplastic. The cytological and histological data was analyzed and compared with peer studies

Inclusion criteria

180 cases of histopathology reported as nodular goiters were included in the study. Out of 128 cases with cytological data, only 96 cases were included in the correlation study to know the efficacy and accuracy of cytology by taking histopathology as the gold standard test.

Exclusion criteria

Cases with inadequate clinical details, inadequate or inconclusive cytological data were excluded from the study.

Statistical analysis

After studying, histopathological sections, the data collected was analyzed statistically and tabulated.

Descriptive statistics was adopted to analyse the study data using percentage, tables, graphs, bar diagrams, line diagrams and pie charts.

Inferential statistics consisting of Chi-square, sensitivity, specificity and accuracy were used to analyse the diagnostic efficacy of cytology with that of histopathology.

These cases were considered to be false negative or false positive based on the definitions established by the Papanicolaou Society of Cytopathology. A false – negative (FN) diagnosis is defined as cytologic interpretation of non-neoplastic lesion, which would otherwise, have not had required surgical excisions, yet the resection revealed a malignant lesion. A false – positive (FP) diagnosis is defined as a cytologic diagnosis of neoplasm requiring surgical excision, but appeared to be a non-neoplastic lesion in the subsequent surgical resection. A true – positive (TP) result for a neoplasm is the one with subsequent final histopathological verification for the presence of a neoplastic process. A true – negative (TN) result is the one with no evidence of a neoplastic process on cytology with subsequent final histopathological confirmation.

Results

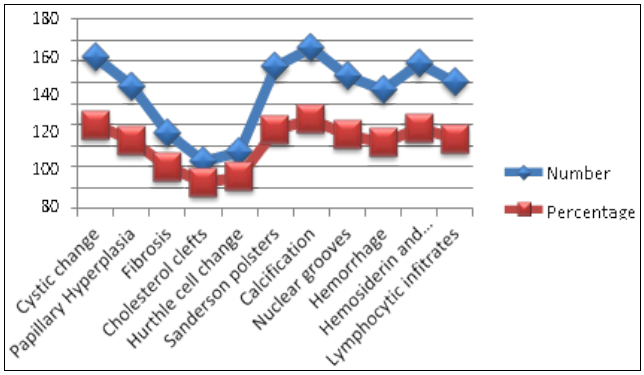

Chart 1: Morphological patterns seen in nodular thyroid lesion

Various morphological patterns were noted; most common were calcification (85%), cystic change (80%) and Sanderson polsters (75%).

Table 1: List of ambiguous HPE diagnosis given in this study with their age and sex distribution

Ambiguous lesions	Age	Sex
Follicular Adenoma / MNG	55	F
Follicular Adenoma / MNG	40	F
Follicular Adenoma / MNG	42	F
Suspicious of Papillary neoplasm	54	F
Follicular tumor of uncertain malignant potential	55	F

Ambiguous lesions reported in this study were Follicular tumor of uncertain malignant potential and suspicious of papillary neoplasm in the middle aged women. Follicular adenoma and MNG were difficult to distinguish in three cases due to extensive cystic and clear cell change.

Table 2: Age distribution of nonneoplastic lesions associated with nodular goiter

Age group	Hashimoto's	Lymphocytic	Riedel's	Graves
0-20	2	0	0	0
21-40	2	0	1	1
41-60	13	3	0	0
61-80	2	0	0	0

19 nonneoplastic lesions associated with MNG were noted in this study i.e. Hashimoto's thyroiditis, Lymphocytic thyroiditis, Riedel's thyroiditis and Graves'. Most common lesion noted was Hashimoto's thyroiditis constituting 19 cases seen in the age group of 41-60 yrs.

Table 3: Age distribution of benign neoplasms associated with nodular goiter

Age group	Follicular Adenoma	Hurthle Cell Adenoma
0-20	0	0
21-40	7	3
41-60	3	1
61-80	1	0

15 benign lesions associated with nodular goiter were noted in this study. They were Follicular adenoma and oncocytic variant or Hurthle cell adenoma. Benign lesions were seen most commonly in 21-40 yrs. age group.

Table 4: Age distribution of malignant lesions associated with nodular goiter

Age group	PTC	Pap micro	Follicular variant	FCT	HCT	MCT
0-20	0	0	0	0	0	0
21-40	4	3	0	0	0	1
41-60	3	2	1	2	0	0
61-80	3	1	1	0	1	0
81-100	0	0	0	0	0	0

22 malignant lesions were observed to be associated with nodular goiter with most common malignant lesion being papillary thyroid carcinoma followed by its variant papillary micro-carcinoma. Both were seen most commonly in the age group of 21-60 yrs. 2 cases of FTC were noted in adults (41-60yrs.) and 2 cases of FVPTC were seen, one in adult (41-60yrs.) and other in elderly age group (61-80yrs.).
The most common age group presenting with malignancy was 41-60 yrs. followed by 21- 40 yrs.
All the nonneoplastic lesions showed a strong female preponderance. Only one case of lymphocytic thyroiditis was reported in a in a male.

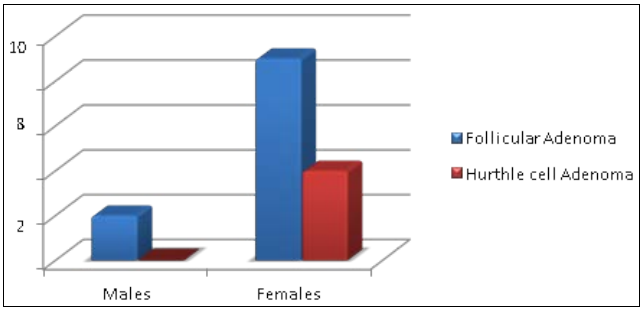

Chart 2: Sex distribution of benign neoplasms associated with nodular goiter

Malignant lesions were found more commonly in females than in males. Females constituted 20 cases in 22 malignant lesions that were reported.
Males constituted only 2 cases. One case reported as papillary carcinoma and the other one as Follicular carcinoma.

Table 5: Categorization of malignant lesions with respect to lymphnodal involvement

Lymph nodes	No of cases
N0	13
N1a	7
N1b	2

The malignant lesions had lymphnodal enlargement with metastases in 9 cases constituting 7 cases of N1a and 2 cases of N1b (WHO Classification)

Malignancies with metastasis
Only one case of follicular carcinoma presented with metastasis to vertebral bone and other case of papillary micro-carcinoma that showed skin infiltration. All others were free of metastasis at the time of thyroidectomy. Follow up couldn't be made as patients come from different areas to the institute and because of the practical difficulties associated with the task.

Table 6: Categorization according to the "International system - The Bethesda system for reporting thyroid cytology" (TBSRTC)-

	Cat I	Cat II	Cat III	Cat IV	Cat V	Cat VI
No of cases	10	81	7	17	3	10

According to the International system, i.e. TBSRTC – The Bethesda system of reporting thyroid cytology, the cases (128) with recorded cytological data were graded.
Category – I included 10 cases with inadequate smears for reporting. Most of them i.e. 81 cases constituting 63.28% were benign and were included under Category II. Only 7 cases were indeterminate lesions. Category IV included the next highest reported cases after Category II including 17 cases constituting 13.28%. Only 3 cases were included under suspicious category/category V. 7.8% i.e. 10 cases were reported to be malignant.

Discussion

Table 7: Categorization of FNAC of thyroid lesions according to Bethesda system (TBSRTC) with respect to other studies

Category	Present study	KUKAR *et al.*[4]	Gharibh *et al.* [5]	Hyang Mi KO *et al.* [6]
I	7.81%	3.9%	21%	5%
II	63.28%	70.4%	64%	83.4%
III	5.46%	17.2%	11%	2.7%
IV	13.28%			1.6%
V	2.34%			
VI	7.81%	8.5%	4%	7.3%

Present study showed 83% benign lesions which was in concordance with other studies. Similar to Kukar *et al.* [4] (70.4%), Gharibh *et al.* [5] (64%) and Hyang MiKo *et al.* [6] (83.4%).
Indeterminate lesions comprised 5.46% in the present study relatively more compared with Hyang Mi KO *et al.* [6] study that showed 2.7%.
Mandreker *et al.* [7] found a high incidence of inadequate samples when the cytopathologist does not perform the FNA.
The variability of various lesions could be due to studies being conducted on different population of various countries and variable influences of geographical, environment, dietary and hereditary factors.

Table 8: Nonneoplastic lesions associated with nodular goiter in comparison with other studies

Characteristics	Present study	Eranga Himalee *et al.* [8]
Total No of Cases	180	349
Hashimoto's thyroiditis	10.55%	9.9%

Present study showed 11% nonneoplastic cases associated with MNG which included Hashimoto's thyroiditis (10.55%) (Figure-14, 15, 16), Lymphocytic thyroiditis (1.66%) (Figure- 17, 18, 19), Riedel's thyroiditis (0.5%). (Figures- 12, 13) and Graves' disease (0.5%) (Figures – 20, 21, 22). Our study showed Hashimoto's thyroiditis as the most common nonneoplastic lesion (10.55%) associated with MNG similar to Eranga himalee *et al.* [8] study (9.9%).

Table 9: Distribution of benign lesions associated with nodular goiter in comparison with other studies

Benign neoplasms	Present study	Karhik Kathladka *et al.* [9]	Padmawar *et al.* [10]
Follicular adenoma	11(6.1%)	6(6%)	2(3.50)
Hurthle cell adenoma	4(2.2%)	-	-

Present study showed incidence of follicular adenoma (Figures – 26, 27) to be 6.1% (11cases) similar to Karthik Kathladka *et al.* [9] study (6%). In contrast, Padmawar *et al.* [10] showed considerably low incidence of follicular adenoma with only 3.5% cases. Hurthle cell adenoma (2.2%) (Figure – 28, 29) was noted only in this study in contrast to other studies.

Table 10: Distribution of malignant lesions associated with nodular goiter with comparison to other studies

Malignancy	Present study	Padmawar *et al.* [10]	Hanuma nthappa. *et al.* [11]	Chetan VR *et al.* [12]	Sengupta *et al.* [13]	Htwe TT *et al.* [14]
PTC	10(5.5%)	6(10.52)	6(6%)	9(12.3%)	9(5.42%)	33(4.0%)
Papillary micro	6(3.3%)	-	-	-	-	-
FVPTC	2(1.1%)	-	-	-	-	6(0.7%)
FTC	2(1.1%)	-	2(2%)	3(4.1%)	7(4.2%)	14(1.7%)
HCC	1(0.5%)	-	1(1%)	-	-	-
MTC	1(0.5%)	1(1.75%)	1(1%)	-	1(0.60%)	-

Present study showed an incidence of 12.22% malignant lesions in 180 cases taken for study similar to Prades *et al.* [14] (12.22%), Hanumanthappa *et al.* [11] (10%), Benzarti *et al.* [15] (9.5%). A long standing and hitherto unresolved issue is whether MNG is significantly associated with malignancy. MNG has been traditionally thought to be at a low risk for malignancy as compared to a solitary nodule thyroid. However, various studies showed that the risk was quite high in MNG also [11].

In the present study, most common carcinoma associated with MNG was found to be papillary thyroid carcinoma comprising 10 cases (5.55%) similar to the studies by Hanumanthappa *et al.* [11] (6%).

Chetan VR *et al.* [12] (12.3%), Padmawar *et al.* [10] (10.52%) showed more incidence of PTC in their studies compared to present study (5.5%).

2Cases of follicular carcinoma with 1.1% were noted in present study which was similar to Hanumanthappa *et al.* [11] (2%) study. A relatively more prevalence of follicular carcinoma was found in Sengupta *et al.* [81] (4.21%) and Chetan VR *et al.* [12] (4.1%) studies.

2cases (1.1%) of Follicular variant of papillary carcinoma were noted in the present study which was similar to Htwe TT *et al.* [14] (0.7%) study.

Incidence of Hurthle cell carcinoma and medullary carcinoma was relatively low in the present study (0.5% each). These findings were concordant with Hanumanthappa *et al.* [11] study.

There is a changing trend towards more frequent occurrence of PTC compared to FCT and this may be attributable to widespread iodization programs.16 Data from The Indian Council of Medical research also established that the commonest cancer type is PTC, followed by Follicular carcinoma [17].

Present study showed incidence of malignancy i.e. 12.22% in concordance with Chetan V R *et al.* [12], a Nellore based study that showed 16.5% malignancy.

Chetan V R *et al.* [12] and the present study were studies done in Andhra Pradesh region, Nellore being more coastally located than Guntur presented with higher frequency of malignancy.

Sengupta *et al.* [13], study in Sikkim showed 12.65% malignancy incidence. However, Padmawar10 *et al.* study revealed 20% malignancy in Wardha, a region of Maharashtra.

(Abbreviations – MNG – Multi-nodular Goitre, NG – Nodular goitre, FNAC –

Fine needle aspiration cytology, FN – Follicular neoplasm, PN – Papillary neoplasm, PTC – Papillary thyroid carcinoma, FCT – Follicular carcinoma thyroid, HCA – Hurthle cell adenoma, FVPTC – Follicular variant of Papillary thyroid carcinoma, DN – Dominant nodule, MCT – Medullary carcinoma thyroid, HCC – Hurthle cell Carcinoma, Hashi – Hashimoto's thyroiditis, LT – lymphocytic thyroiditis, FAD – Follicular adenoma.

Table 11: The cytological grading and histopathology report

Cytology		Histopathology	
Diagnosis	**No. (%)**	**Diagnosis**	**Number (%)**
Benign (Category II)	81(63.28%)	1. MNG –	58(71.60%)
		2. MNG + HASHI-	5 (6.1%)
		3. MNG + FAD/DN-	9 (11.1%)
		4. MNG + LT	1 (1.23%)
		5. Pap micro	2 (2.4%)
		6. MNG + PTC	3 (3.7%)
		7. MNG + SUSPISCIOUS PN	1 (1.23%)
		8. HCA	2 (2.4%)
Indeterminate (Category III)	7(5.4%)	1. MNG-	5 (71.4%)
		2. FAD-	1 (14.2%)
		3. MNG + HASHI-	1 (14.2%)
Follicular neoplasm (Category IV)	17(13.28%)	1. FAD/FAD (ONCO)	3 (23.5%)
		2. FAD, Hashi & MNG	1 (5.8%)
		3. FTUMP	1 (5.8%)
		4. MNG – DN/MNG	7 (41.1%)
		5. MNG - HASHI	3 (17.6%)
		6. MNG- LT	1 (5.8%)
		7. HCC	1 (5.8%)
Suspicious (Category V)	3(2.34%)	1. MNG	1 (33.33%)
		2. FCT	1 (33.33%)
		3. Pap micro	1 (33.33%)
Malignancy (Category VI)	10(7.8%)	1. PTC	4 (40%)
		2. Pap micro	1 (10%)
		3. FVPTC	1 (10%)
		4. MCT	1 (10%)
		5. MNG	3 (30%)

Above table depicts the variations in the cytology and histopathology reports.

Also, the table depicts the nature of lesions in histopathology with respect to cytological grading of the thyroid lesions. 2cases of PTC and 2 cases of papillary micro-carcinoma were found in the cases reported in cytology as benign. Single case of suspicious of papillary neoplasm was seen in HPE due to ambiguous histological features that were reported as Benign Category II lesion in Cytology.

These cases were misdiagnosed in cytology in the vicinity of micro- nodules for which the target lesion is something other than micro-foci of PTC. Some pathologists do not consider these “incidental nodules” as true “false negative” cases, as their nature can only be proven to be “false negative”, if they are truly clinically significant lesions on surgical excision. However, some of these “micro-carcinomas” can be clinically meaningful lesions as shown by Yang95and colleagues in their series. Indeterminate cases i.e. category III lesions in the study showed only benign lesions in histopathology. No malignancy was reported in them.

Category IV lesions in cytology showed mostly benign lesions, a case was termed as Follicular lesion of uncertain malignant potential (FTUMP) due to suspicious features and questionable capsular invasion. A case of Hurthle cell carcinoma in HPE was reported as Follicular neoplasm – Category IV lesion.

Cytological distinction between these conditions is often difficult due to the presence of various overlapping cytological features. Architectural pattern and honeycomb sheets of adenomatous goiter versus syncytial type fragments with crowding of nuclei with irregular follicles of follicular neoplasm, is an important criterion that distinguishes the two entities.

3 suspicious cases were reported as Category V lesions, out of which one showed Follicular carcinoma thyroid, one PTC and the other one was found to be benign in HPE.

7 out of 10 Category VI lesions showed evidence of malignancy in HPE that included 4 PTC, 1 papillary micro-carcinoma, 1 FVPTC, 1 MCT and 3 false positive cases were reported.

Cytological diagnosis of papillary carcinoma was made, on the basis of excess of cellularity with plenty of papillae, few of the cells contained round nucleus, pale open chromatin and intranuclear inclusion.

Table 12: Critical evaluation of false positive and false negative cases in cytology

False – positive cases		
Cytological findings	**Histopathology findings**	**Comments**
Follicular patterned smears Follicular neoplasm	- MNG - MNG with Hashimoto's thyroiditis - MNG with Dominant nodule	Emphasis on cellularity, overlooked the architectural honeycomb pattern
Papillary patterned smears Papillary thyroid carcinoma	- Papillary hyperplasia and cystic change in Nodular goitre.	Emphasis on cellularity and architectural patterns without cytomorphology of papillary carcinoma; Pseudopsammoma body (inspissated colloid within follicles)
False positive cases		
Cytological findings	**Histopathological findings**	**Comments**
Lymphocyte rich smears Follicular neoplasm	MNG with Lymphocytic thyroiditis	Sampling error; Overlooked presence of lymphocytic background
Hurthle cell rich smears Follicular neoplasm	MNG with focal Hurthle cell change	Sampling error; Failure to appreciate the non- neoplastic nature of cells and few Hurthle cells in the background of moderate colloid
False – negative cases		
Cytological Findings	**Histopathological findings**	**Comments**
Colloid adenomatous goitre	- Papillary thyroid Carcinoma	Missing the target lesions/ Lack of architectural features and inability to appreciate nuclear features
MNG with cystic change	- Papillary micro Carcinoma	Sampling error, Inexperience in recognizing the minimal cytological atypia.

Conclusion

The reported results of preoperative diagnostic techniques in literature are a source of optimism for surgeons looking for rational, safe and efficient strategies to manage thyroid nodules. Epidemiological variation implicates the need for more research as coastal and high altitude areas differ from others in the incidence of malignancy and presentation of thyroid lesions. This requires both local research and protocols which include standardization of ultrasound reporting, implementation of Bethesda system of reporting thyroid cytology and improvements in biopsy techniques. As these are implemented, they may add another arm to the diagnostic algorithm currently available to us and avoid unwanted surgeries.

Acknowledgment

The author thankful to Department of Pathology for providing all the facilities to carry out this work.

Conflict of Interest

None

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