

Observational Study on Clinicopathological Spectrum of Thyroid Lesions in Tertiary Cancer Care Centre at Marathwada Region of Maharashtra, India

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ABSTRACT

Introduction: The thyroid has the potential to develop variety of non-neoplastic lesions as well as benign and malignant neoplasms. Thyroid gland may be affected by various disorders like developmental, inflammatory, hyperplastic and neoplastic conditions. The follicular-derived neoplasm is the most common type of thyroid neoplasm. In the new edition of World Health Organisation (WHO) classification 2017, it could be identified as benign follicular tumours (follicular adenoma, hyalinising trabecular tumour), borderline follicular tumours (Follicular Tumour of Uncertain Malignant Potential (FT-UMP), Well-Differentiated Tumour of Uncertain Malignant Potential (WDT-UMP), and Non-invasive Follicular Thyroid Neoplasm with Papillary Nuclear Features (NIFTP)), papillary carcinoma, follicular carcinoma. Considering wide variation and several borderline and uncertain potentially malignant cases in the present observational study, authors analysed all the spectrum of thyroid lesions which included lymphoma, goiter, anaplastic carcinoma, metastatic carcinoma to thyroid gland, NIFTP etc., apart from thyroid malignancies encountered commonly.

Aim: To study histopathological features of spectrum of thyroid lesions; both non-neoplastic and neoplastic.

Materials and Methods: Present retrospective observational descriptive study was carried out at Department of Pathology, Tertiary

Care Cancer Hospital in Marathwada region of Maharashtra, India, from January 2018 to September 2020. Total 84 patients who had undergone thyroidectomy were included in the analysis. Patient's clinical details like age, radiological findings, tumour marker studies, if any were taken into consideration before evaluating specimens and slides.

Results: Clinically, all 84 cases presented with swelling on anterior aspect of neck. Radiological features were not evaluated pertaining to lack of electronic medical records at the hospital. Results were analysed for multiple parameters like age, sex, lymph node involvement, type of thyroid malignancies, presence of parathyroid gland, etc. Female preponderance was noted in all thyroid lesions including malignancies, out of 84 patients, 64 were females and 20 were males. Out of 84 cases studied, 26 cases were of papillary thyroid carcinoma; followed by 21 cases showing non-neoplastic thyroid swelling like colloid goiter, multinodular goiter or thyroiditis. Carcinoma cases were more in number than goiter in present study, pertaining to our centre being Tertiary Care Cancer Centre.

Conclusion: Histopathology evaluation of specimen's remains gold standard for diagnosis however, it has to be interpreted on the background of clinical and radiological data. IHC studies though rarely needed are useful in cases of anaplastic carcinoma, lymphoma and metastasis to thyroid.

Keywords: Anaplastic, Lymphoma, Goiter

INTRODUCTION

The thyroid has potential to develop variety of non-neoplastic lesions as well as benign and malignant neoplasm's. Thyroid swelling is still prevalent, and patient may usually present due to cosmetic reasons. Thyroid gland may be affected by various disorders like developmental, inflammatory, hyperplastic and neoplastic conditions. Diagnostic tools are available for patients with thyroid nodule includes clinical examination, Thyroid Stimulating Hormone (TSH) levels, ultrasonography, thyroid scan, Fine Needle Aspiration Cytology (FNAC), however histopathologic evaluation of specimen remains gold standard. Apart from that ancillary techniques like immunohistochemistry (IHC) studies, tumour marker studies and molecular studies are important particularly when findings on histopathology are equivocal.

In 2017, the WHO classification [1] of tumours of endocrine organs established criteria for new entity called Non-invasive follicular tumour with papillary like nuclear features. The follicular-derived neoplasm is the most common type of thyroid neoplasm. In the new edition of WHO classification 2017 [1], it could be identified as benign follicular tumours (follicular adenoma, hyalinising trabecular tumour), borderline follicular tumours (FT-UMP, WDT-UMP, and

NIFTP), papillary carcinoma, follicular carcinoma. Carcinoma of thyroid is most common endocrine cancer and its incidence has continuously increased in last three decades [2]. Apart from usual papillary carcinoma and follicular neoplasms, some rare and newer entities were noted in the present study. These are new entities which cause diagnostic difficulty on histopathology particularly on frozen sections due to limited sampling. Primary thyroid lymphoma is a rare condition accounting for 1 to 5% of all thyroid malignancies and approximately 2% of all extranodal lymphoma [3]. Although mortality is less in thyroid cancer, anaplastic thyroid carcinoma accounts for 14-39% of thyroid carcinoma deaths [4].

The present study observed the spectrum of thyroid lesions which included rare entities like lymphoma, anaplastic carcinoma, metastasis to thyroid gland, NIFTP etc., apart from routine thyroid malignancies encountered commonly were analysed.

MATERIALS AND METHODS

Present study was a retrospective observational descriptive study which was carried out in Department of Pathology, Tertiary Care Cancer Hospital in Marathwada region of Maharashtra, India. Ethical approval was obtained for the study from Institutional Ethical

Committee (IEC) with approval number IEC/GMCA/006/2021. Cases included from January 2018 to September 2020; which included evaluation of 84 successive thyroidectomy specimens. The records of the Department of Pathology, histopathology section of Tertiary Care Cancer Hospital, were searched and all patients with thyroid lesions were studied. Total 84 patients who had undergone thyroidectomy were included in the analysis. Patients clinical details like age, radiological findings, tumour marker studies if any were taken into consideration before evaluating specimens and slides. Since, it was non-interventional observational study, no prior consent was taken from patients.

Exclusion criteria are slides or blocks received from outside for review or second opinion were excluded from study.

Specimen were examined and fixed in 10% neutral buffered formalin; external surface was inked with the water proof acrylic ink; thorough sampling and multiple sections were given in cases where capsular invasion was suspected. Sections (5 µm) cut from paraffin-embedded specimens and stained with Haematoxylin and Eosin (H&E) were examined and reported in final histopathology reports. All the parameters required as core data element like angiolymphatic invasion, perineural invasion, vascular invasion, presence of parathyroid tissue, extrathyroidal extension were reported as per standard protocols. Deep cut and serial sections to demonstrate capsular or vascular invasion in follicular carcinoma were studied when findings were questionable or equivocal.

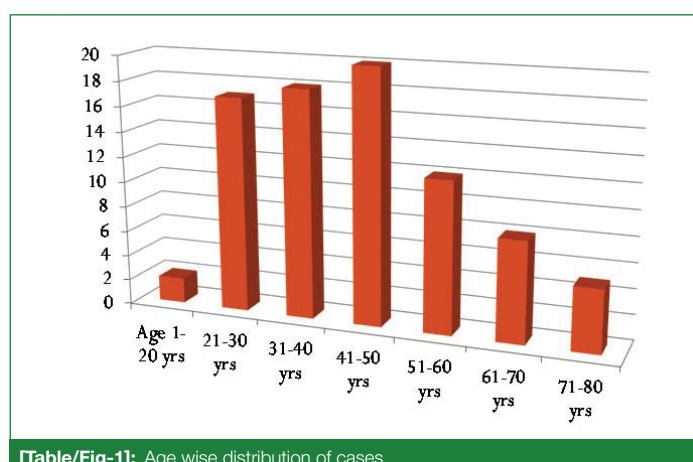
IHC study was required in cases of lymphoma, anaplastic thyroid carcinoma, metastasis to thyroid from breast primary and findings of IHC were concordant to routine morphology findings in all these cases. Panel of lymphoma markers like CD10, CD20, CD3 and CD23 (Cluster of Differentiation) were used. In case of breast carcinoma metastatic to thyroid ER (Estrogen Receptor), PR (Progesterone Receptor) and Human Epidermal Growth Receptor 2 (HER2/neu) were used. Pan CK (Cytokeratin), vimentin, Thyroid Transcription Factor (TTF1) were used in anaplastic carcinoma of thyroid.

STATISTICAL ANALYSIS

Data was tabulated as percentages and no statistical test was applied.

RESULTS

Age wise distribution: Youngest age patient presented with thyroid swelling was 16 years male and oldest patient was 76 years male. Most common age group with thyroid lesions were between 41-50 years age [Table/Fig-1].



[Table/Fig-1]: Age wise distribution of cases.

Sex wise distribution: Female preponderance of 76% was noted in all thyroid lesions including malignancies. Male to female ratio was 1:3.2.

Spectrum of thyroid lesions: Papillary carcinoma of thyroid was commonest lesion found in all thyroidectomy specimens received. Out of 84 cases studied, 26 cases were of papillary

thyroid carcinoma; followed by 21 cases showing non-neoplastic thyroid swelling like colloid goiter, multinodular goiter or thyroiditis. Carcinoma cases were more in number than goiter in present study, pertaining to our centre being Tertiary Care Cancer Centre and many cases diagnosed outside as carcinoma are referred for further management and thyroidectomy at our centre. Eight cases were of complete thyroidectomy in which no residual tumour was found on thorough sampling [Table/Fig-2]. One case of follicular carcinoma presented with mandibular swelling and mandibulectomy was done which revealed metastasis from follicular carcinoma of thyroid. In one case of thyroidectomy revealed metastatic deposits of carcinoma, on studying clinical details, patient was known case of carcinoma (Ca) breast presented with thyroid swelling and diagnosis of metastatic deposits of breast carcinoma to thyroid was offered. Smallest tumour size was noted in papillary carcinoma of thyroid measuring microscopic focus of tumour of size 0.5 × 0.3 cm.

Thyroid lesion category	Number of cases (%)
Papillary carcinoma of thyroid	26 (30.95)
Follicular carcinoma of thyroid	4 (4.76)
Medullary carcinoma of thyroid	4 (4.76)
Anaplastic carcinoma of thyroid	2 (2.38)
Primary thyroid lymphoma	2 (2.38)
NIFTP- Noninvasive follicular thyroid neoplasm with papillary like nuclear features	3 (3.57)
Follicular adenoma	13 (15.47)
Goiter and thyroiditis	21 (25)
Metastasis in thyroid	1 (From breast primary)

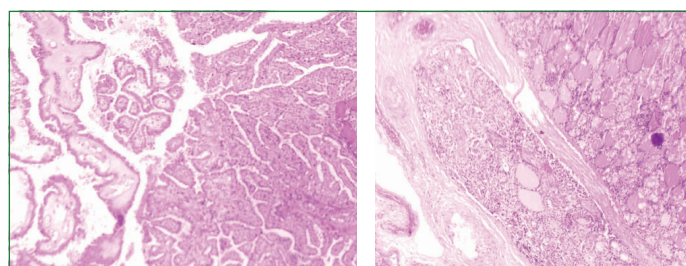
[Table/Fig-2]: Distribution of thyroid cases in present study.

Status of Lymph nodes

Lymph nodes dissection was performed with various procedures like modified radical neck dissection, central compartment neck dissection. Apart from level I to level V positivity was seen in various cases, there was lymph node involvement by papillary carcinoma of thyroid in Level VI in one case [Table/Fig-3]. Paratracheal, superior mediastinal and right recurrent laryngeal lymph nodes were sent separately by operating surgeon in three different cases also revealed metastasis from papillary carcinoma of thyroid. Haematoxylin and Eosin staining of various carcinoma is shown in [Table/Fig-4-9], whereas gross image in case of follicular carcinoma of thyroid is shown in [Table/Fig-10].

Type of carcinoma	Lymph node positivity
Papillary carcinoma	18 out of 26 cases showed lymph node metastasis.
Medullary carcinoma	2 out of 4 cases showed lymph node metastasis.
Follicular carcinoma	1 out of 4 cases showed lymph node metastasis.
Anaplastic carcinoma	1 out of 2 cases showed lymph node metastasis.

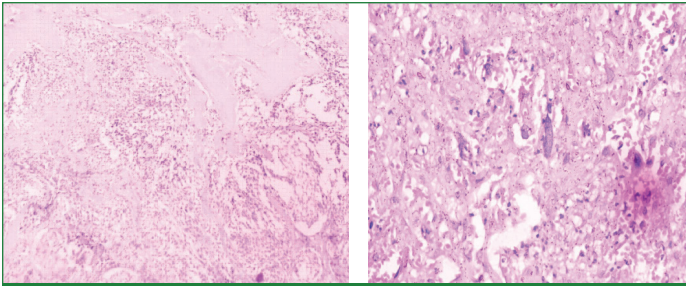
[Table/Fig-3]: Distribution of thyroid malignancies and lymph node positivity.



[Table/Fig-4]: Conventional papillary carcinoma of thyroid; papillary structures with optically clear nuclei seen. (H&E stain; 10x magnification)

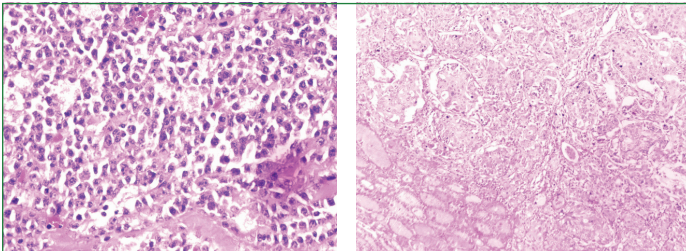
[Table/Fig-5]: Follicular carcinoma of thyroid; capsular invasion is evident. (H&E stain; 10x magnification) (Images from left to right)

Central compartment dissection was performed in five cases which showed tumour deposits. Largest nodal metastatic mass of size 6.5 cm was seen in one case. Such higher rate of lymph node



[Table/Fig-6]: Medullary carcinoma of thyroid; eosinophilic amyloid material seen. (H&E stain; 10x magnification)

[Table/Fig-7]: Anaplastic carcinoma of thyroid. Large areas of necrosis with few bizarre cells. (H&E stain; 10x magnification) (Images from left to right)



[Table/Fig-8]: Lymphoma of thyroid; diffuse sheets of round lymphoid cells.

[Table/Fig-9]: Metastasis from ductal carcinoma breast in thyroid. (H&E stain; 10x magnification) (Images from left to right)



[Table/Fig-10]: On cut-section left lobe show multiple whitish firm nodules abutting thyroid capsule and entirely involving the left lobe in case of follicular carcinoma of thyroid.

involvement may be attributed to patients presenting late with disease in our locality.

Extrathyroidal extension in papillary carcinoma was seen in two cases in present study, of which one case showed involvement of larynx by papillary carcinoma of thyroid.

Presence of incidental parathyroid tissue was noted in 15 cases of thyroidectomy; parathyroid was unremarkable microscopically. In all cases parathyroid tissue were located on extracapsular location.

IHC study: Role of IHC was minimal in cases of thyroid malignancies.

1) IHC findings in present study was carried out in three cases as follows: (IHC studies were outsourced); 2) Anaplastic carcinoma revealed: Pan CK: focally positive; VIMENTIN, TTF1, CK19: positive and CK5/6: negative and diagnosis of undifferentiated anaplastic sarcomatoid carcinoma of thyroid was offered; 3) IHC findings in case of lymphoma were as: Positive for CD 20 and CD 10 and focal positivity for CD23 and Negative for CD3, BCL2 and BCL 6. Diagnosis of Diffuse Large B-Cell Lymphoma (DLBCL) in the background of hashimoto's thyroiditis was offered on IHC. It confirmed our morphology diagnosis of primary thyroid lymphoma; 4) IHC finding in case of metastatic breast carcinoma to thyroid revealed ER, PR negative and HER2/neu positivity and EGFR was moderate to strong positive in 10% of tumour cells.

DISCUSSION

In present study, most common age group affected was between 41-50 years, this finding was concordant with study carried out by Shah AA et al., while in study carried out by Jain S et al., most common age group was between 31-40 years [5,6]. In present study, females are more affected than males, this finding is concordant

with studies carried by Shah AA et al., and Borsaikia K et al., [6,7]. Female to male ratio in present study was 3.2:1.

The Surveillance, Epidemiology and End Results (SEER) database shows median age at 50 years and United Kingdom database shows median age at 40-44 years [8,9] and present study results were concordant with these database with most common age group affected was between 41-50 years. Similarly the SEER database UK database show thyroid carcinoma are more common in females and also study carried out by Parikh HK et al., reported that thyroid carcinoma is five times more common in females [8-10].

Papillary carcinoma was most common histological pattern of thyroid lesions; in present study, 30.95% of cases were of papillary carcinoma thyroid while 25% cases were of non-neoplastic conditions like goiter or thyroiditis. This finding of more number of neoplasms may be attributed to our center being Tertiary Care Cancer Hospital with many diagnosed cases of thyroid malignancies are referred for further management. In contrast of the study carried out by Borsaikia K and Patil M revealed, most cases of colloid goiter followed by thyroiditis and study carried by Kumbhar S and Kanetkar S showed 70% of cases with non-neoplastic conditions and 30 % cases were neoplasms [7,11].

Metastasis to thyroid is extremely rare although being vascular organ, in present study only one case was of metastasis to thyroid from a case of carcinoma breast (ductal carcinoma), [Table/Fig-10]. This finding was similar with findings of Shah AA et al., in their study also only one case was presented with metastasis to thyroid [5]. Metastasis to thyroid gland is uncommon and is mostly from kidney, GI tract, lungs, skin and rarely breast [12,13]. These are usually associated with poor prognosis. Patient of thyroid swelling with past history of malignancy elsewhere in body, suspicion of metastatic disease should be raised and thyroidectomy can be considered for local disease control.

Papillary carcinoma spreads via lymphatic route whereas follicular carcinoma spreads via hematogenous route. Cervical lymph node metastasis was seen in 69.23% cases in studies carried out by Shah AA et al., it was 54.16% and Wada N et al., reported it to be 69.5%; higher rate of cervical lymph node metastasis may be attributed to late presentation of patients at our centre [5,14].

In a case of follicular carcinoma of thyroid, a 45 year old female came with swelling in mandibular region, hemimandibulectomy revealed metastatic deposits of follicular carcinoma of thyroid and underlying bone and overlying dermis was involved by tumour. Mandibular metastasis due to follicular carcinoma is not very frequent. Mandibular metastasis is most common due to lung primary in men and breast primary in women [15]. In study carried out by Bhadage CJ et al., they observed mandibular swelling as a presenting symptom before diagnosis of primary malignancy of follicular carcinoma of thyroid [16].

Primary lymphoma of thyroid is rare entity, it should be suspected in patients of hashimoto's thyroiditis with rapidly progress in size of neck mass. DLBCL is most common subtype. In present study, two cases were diagnosed with primary thyroid lymphoma [Table/Fig-8] of which one case was 39 years female and IHC in this case proved and confirmed it as DLBCL on the background of hashimoto's thyroiditis. Patients suffering from long standing hashimoto's thyroiditis are at higher risk of developing primary thyroid lymphoma, pathogenesis of lymphoma is probably related with chronic inflammatory stimulation [17]. Lymphoma diagnosis and its confirmation is essential to avoid complex burdensome surgery and chemotherapy is treatment of choice. In a study carried out by Kakkar A et al., they concluded that lymphoma should be suspected in all patients that present with a rapidly enlarging neck mass, particularly females with Hashimoto's thyroiditis [18]. While FNAC is the initial investigative modality, it may not always be diagnostic and histopathological evaluation supplemented by IHC remains the gold standard.

Extrathyroidal extension is defined as a tumour spread outside of thyroid and into surrounding tissues, it plays significant role in outcome of patient, recurrence of disease, and mortality. Extrathyroidal extension in papillary carcinoma was seen in two

cases in present study, of which one case showed involvement of larynx by papillary carcinoma of thyroid [19].

For the specimen that included parathyroid tissue, the slides were scrutinised for the location, the number and histological features of parathyroid gland. Incidental parathyroid excision was defined as microscopic identification of parathyroid gland in thyroidectomy specimen which is distant from benign or malignant thyroid tumour [20]. Delayed presentation of patients with advanced disease and preoperative diagnosis of malignancy make the use of extensive surgical procedures necessary. Attempt to preserve parathyroid gland should be made during thyroid surgeries by meticulous isolating techniques to avoid hypoparathyroidism and morbidity related to it.

A "borderline" tumour group-follicular tumour of uncertain malignant potential, well-differentiated tumour of uncertain malignant potential, and non-invasive follicular thyroid neoplasm with papillary nuclear features-is introduced in the current WHO classification [1]. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features is defined as a non-invasive neoplasm of thyroid follicular cells with follicular pattern and nuclear features like papillary carcinoma of thyroid. The neoplasm is formally classified as non-invasive type (encapsulated) follicular variant of papillary thyroid carcinoma. It is important to examine capsule completely and look for invasion, study deeper section from block before labeling tumour as NIFTP. Since less aggressive management is required in these cases compared to invasive carcinoma and behaviour is also less aggressive.

Anaplastic carcinoma of the thyroid is broadly categorised into 3 patterns: sarcomatoid, giant cell, and epithelial [1]. The carcinoma is positive for cytokeratin TTF-1 is usually negative. In present study, sarcomatoid variant of anaplastic carcinoma was noted which was confirmed on IHC studies.

Limitation(s)

Present study was a retrospective single-centre study, which may limit the generalisation of the findings on a broader scale because of selection bias, lack of follow-up data of these patients due to lack of resources and also no correlation of findings with FNAC which were carried out in many cases preoperatively. Ancillary studies like IHC study were outsourced. Radiological features were not evaluated pertaining to lack of electronic medical records at our hospital.

CONCLUSION(S)

Present study showed spectrum of lesions that can occur in thyroid gland which include non-neoplastic conditions like goiter, thyroiditis and rare neoplastic conditions like lymphoma, anaplastic carcinoma and NIFTP and metastasis to thyroid. Histopathology evaluation of specimens' remains gold standard for diagnosis however, it has to be interpreted on the background of clinical and radiological data. IHC studies though rarely needed, is useful in cases of anaplastic

carcinoma, lymphoma and metastasis to thyroid. In present study, neoplastic lesions were more common than non-neoplastic due to study being conducted at Tertiary Care Cancer Centre. Metastasis to thyroid from invasive breast carcinoma and metastasis to mandible from follicular carcinoma of thyroid are extremely rare were noted in present study.

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