Original Research Article

Spectrum of thyroid neoplasms: A one year study at tertiary referral center

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Abstract

Background: Thyroid cancer accounts for approximately 1% of total cancer cases. Thyroid neoplasms are most common malignant lesions in endocrine system. Their incidence is rapidly increasing in recent times, partially attributed to increased awareness and earlier detection of asymptomatic tumors. They present clinically as nodular or diffuse mass lesions of thyroid similar to non- neoplastic lesions. A wide spectrum of neoplasms is encountered and histopathology evaluation is crucial to establish diagnosis. This study is done to present spectrum of thyroid neoplasms with varied histomorphology at a tertiary care center.

Aim: To study the spectrum of thyroid neoplasms at MNJ Institute of Oncology for over a period of one year with special mention of interesting cases and overview of diagnostic pitfalls encountered.

Materials and methods: All thyroidectomy specimens submitted to Department of Pathology for a period of one year, from October 2017 to September 2018 were included in study. Routine processing and staining along with ancillary techniques where ever necessary were used to arrive at diagnosis.

Results: A total of 104 thyroidectomy specimens were included in the present study. Thyroid cancer was common in females. The most commonly encountered malignancy was Papillary carcinoma, seen in 30-40 years age group. Anaplastic carcinoma was seen in 60-70 years age group.

Conclusion: Papillary carcinoma was most commonly encountered thyroid malignancy followed by medullary and anaplastic carcinoma. Follicular adenoma was the most common benign neoplasm. We have encountered almost the entire spectrum of thyroid neoplasms including the rare variants.

Key words

Thyroid neoplasm, Papillary carcinoma, Anaplastic carcinoma, SETTLE.

Introduction

Diseases of thyroid gland are common and comprise a wide range including deficiency disorders, autoimmune mediated and neoplastic conditions. They either cause a systemic disease or localized abnormality like nodular or diffuse enlargement of thyroid gland. The possibility of neoplasm is major concern in patients who present with nodular mass lesions especially solitary nodules in males and in young people. There is a rapid increase in incidence of thyroid cancers in recent times, attributed to early detection. There also increased incidence seen in all stages and variants of thyroid neoplasms. In the present study, we tried to evaluate histomorphological features of thyroid neoplasms in thyroidectomy specimens with special mention on rare variants.

Materials and methods

A prospective study of thyroidectomy specimens received in the Department of Pathology, MNJ Institute of Oncology, Hyderabad was done for a period of one year, from October 2017 to September 2018. Spectrum of thyroid specimens ranging from lobectomy, hemi-thyroidectomy, total-thyroidectomy were included in study. Relevant clinical details and information regarding pre-operative investigations like USG, FNAC were obtained. All specimens were fixed in 10% formalin, gross features were noted. Representative bits taken and subjected to routine processing and staining with H and E stains. Ancillary studies like IHC were done where ever necessary to arrive at final diagnosis. Thyroid neoplasms were classified on histopathology findings as per WHO classification of thyroid tumors.

Results

A total of 104 thyroid specimens received over a period of one year were analysed. Neoplastic lesions were diagnosed in 87 cases, 17 cases were non neoplastic comprising nodular goiters and Hashimoto's thyroiditis. The overall age range was 10-80 years with the mean age of 45 years. Male to female ratio was 1:3.2 with 25 males and 79 females. The incidence of various thyroid neoplasms was shown in **Table - 1**.

Table - 1: Incidence of various thyroid neoplasms.

Thyroid neoplasm	Females	Males	Total
Papillary carcinoma	52	16	68(78.1%)
Follicular carcinoma	1	1	2 (2.3%)
Anaplastic carcinoma	4	0	4 (4.6%)
Medullary carcinoma	1	3	4 (4.6%)
Poorly differentiated	1	0	1 (1.15%)
SETTEL	1	0	1 (1.15%)
NHL	1	0	1 (1.15%)
Follicular adenoma	4	2	6 (6.9%)

Figure - 1: Gross photograph of Papillary carcinoma thyroid showing grey white tumor with papillary projections.

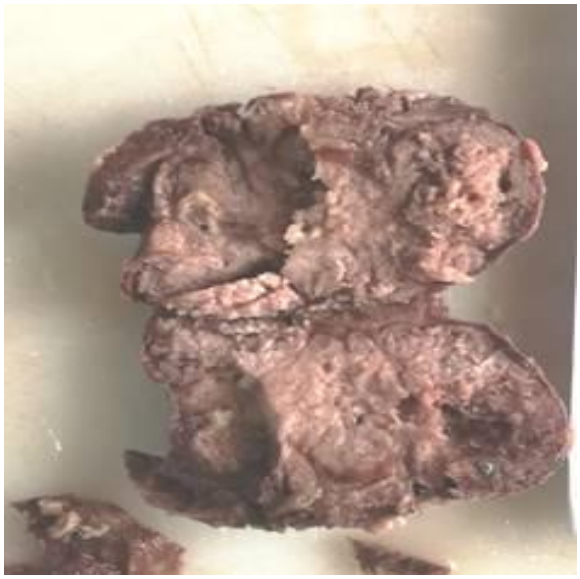
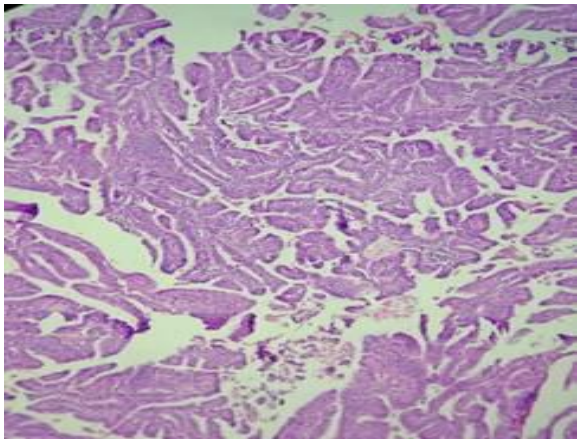


Figure – 2, 3: H&E sections (10X) (40X) showing papillary growth pattern.



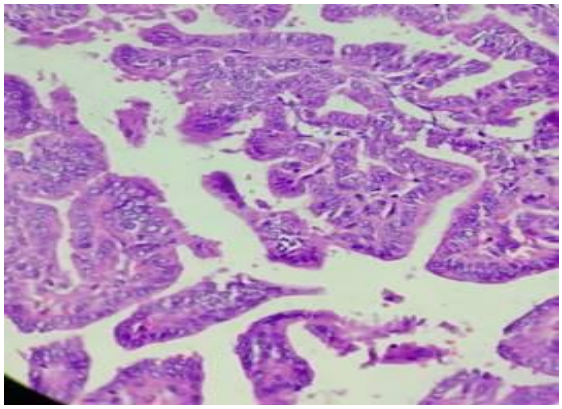


Figure - 4: H&E sections (40X) of FVPTC.

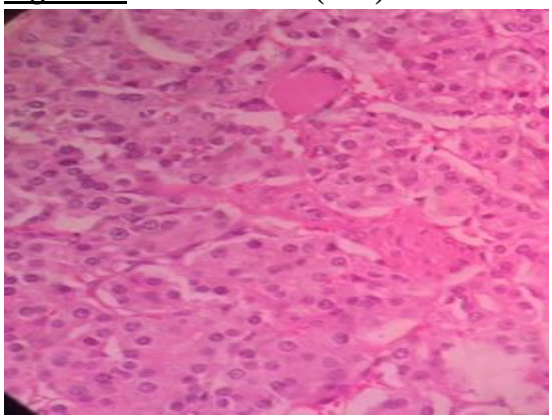
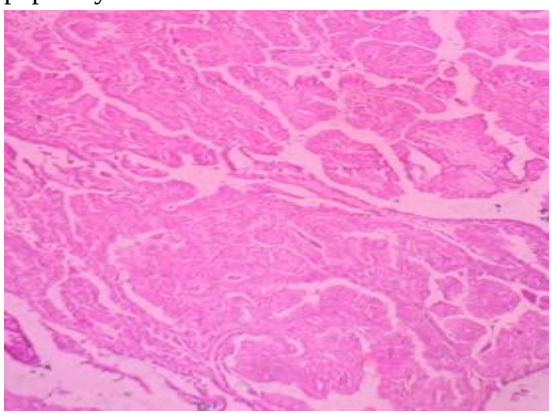
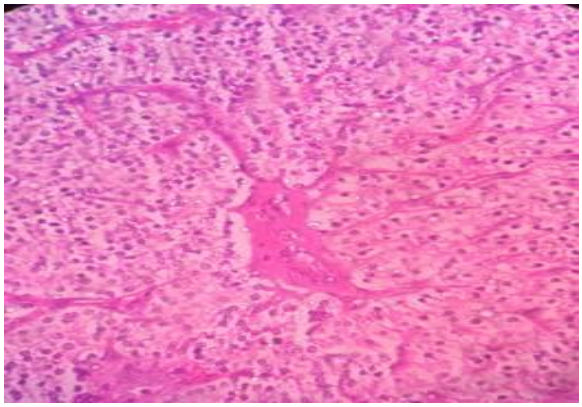


Figure - 5: H&E sections (10X) of Oncocytic papillary carcinoma.

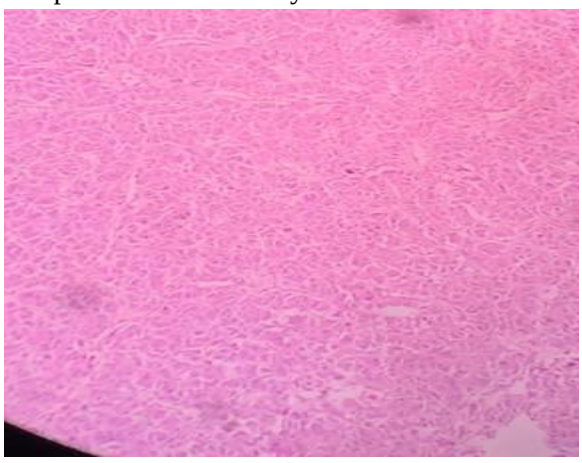


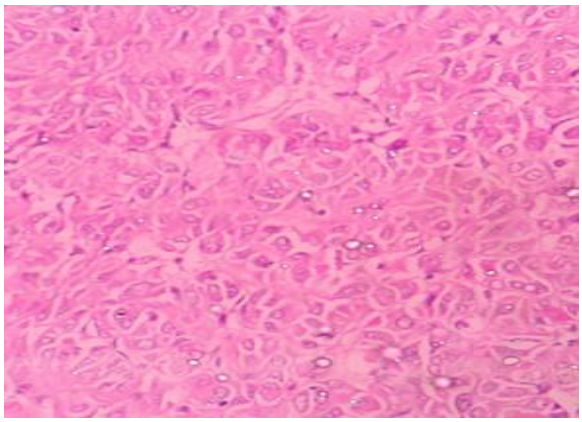
Out of 87 neoplasms, papillary carcinoma was most common and seen in 68 cases (78.1%). Male to female ratio was 1:3.25 with the age range of 10-80 years. Most of the cases clinically presented as nodular swelling or solitary nodule and pre-operativly diagnosed on cytology. Majority of cases had classical papillary growth pattern with characteristic nuclear features of clearing, grooving and intra-nuclear inclusions on histopathology (**Figures - 1, 2, 3**). Among papillary carcinomas diagnosed 16 were follicular variant (FVPTC) (**Figure – 4**), one was oncocytic variant (**Figure – 5**). Almost all cases of FVPTC were infiltrative type with one encapsulated variant.

Figure - 6: H&E sections (10X) of Parathyroid adenoma.



Figures – 7, 8: H&E sections (10X) (40X) showing sheets of pleomorphic cells in Anaplastic carcinoma thyroid.





One female patient aged 45 years who was a known case of non-Hodgkin lymphoma on

treatment, USG neck revealed a small hypoechoic lesion of 1x1.5 cm. Hemithroidectomy was done and was reported as follicular variant of papillary carcinoma. In other case, a female patient aged 46 years total throidectomy was done for papillary carcinoma and revealed concurrent parathyroid adenoma along with papillary carcinoma which is extremely rare (**Figure – 6**). In 16 cases of papillary carcinoma, lymph node metastasis was present at the time of diagnosis and 3 cases presented with nodal recurrence after surgery. Follicular carcinoma was seen in only two cases (2.3%) with capsular and vascular invasion.

Figure - 9: H&E sections (10X) of medullary carcinoma.

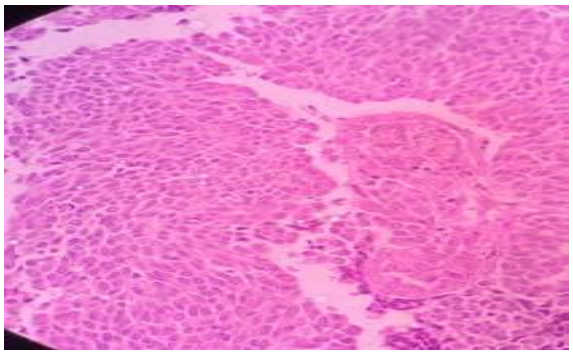
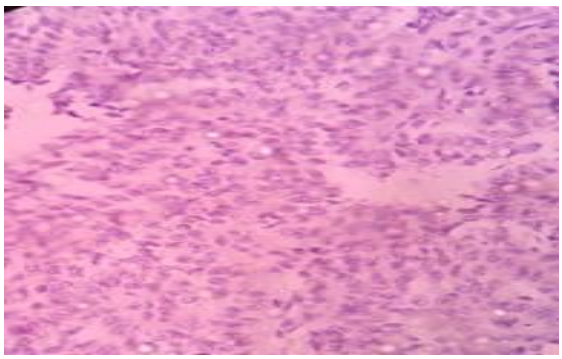


Figure - 10: Negative IHC for TTF-1. Medullary carcinoma.



Anaplastic carcinoma was seen in 4 cases (4.6%), all of them were females aged above 60 years. In 2 cases it was pre operatively diagnosed, but as they were amenable to surgery total thyroidectomy was done. Histopathology sections revealed diffuse sheets of large markedly pleomorphic spindle to oval cells resembling high grade sarcoma with bizzare tumor giant cells, atypical mitotic figures and focal epithelial rests (**Figures - 7, 8**). IHC was done to confirm the diagnosis.

Figure - 11: Positive IHC for PCK. Medullary carcinoma.

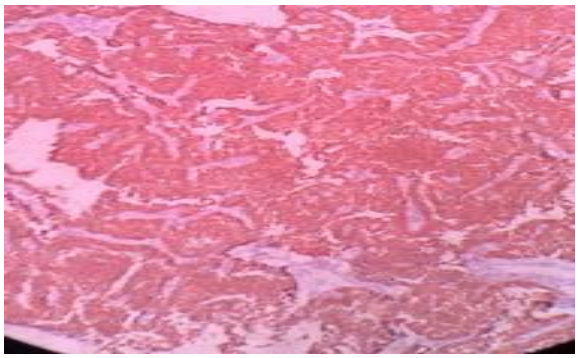


Figure - 12: Positive IHC for Chromogranin. Medullary carcinoma.

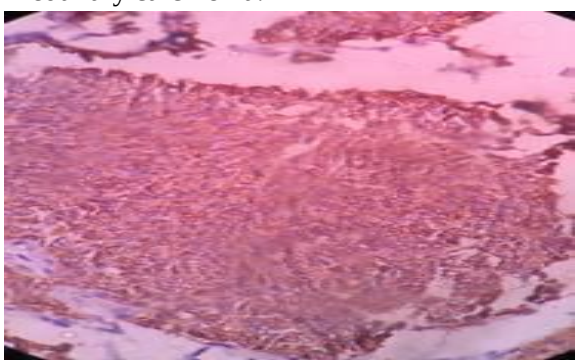
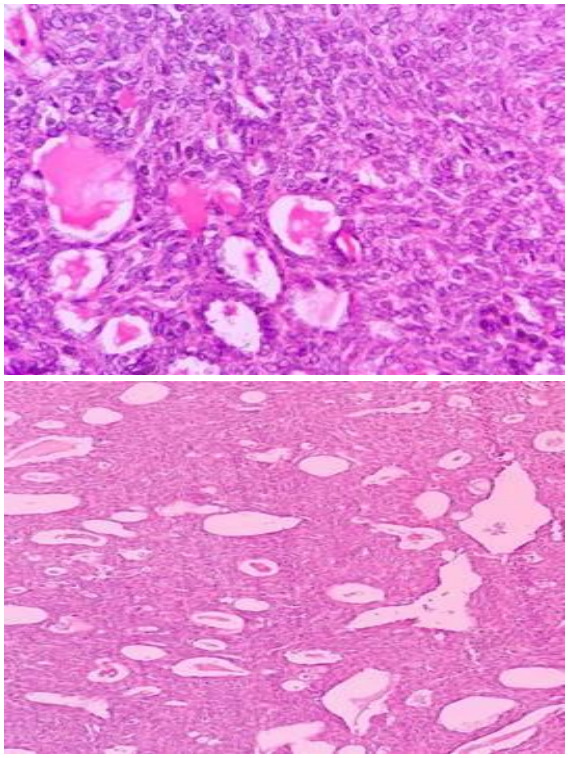


Figure - 13: Gross of SETTLE showing tan gray mass in isthmus.

4 cases (4.6%) were diagnosed as medullary carcinoma with male to female ratio of 3:1. Two patients had increased calcitonin levels. Microscopically, tumor cell arrangement was

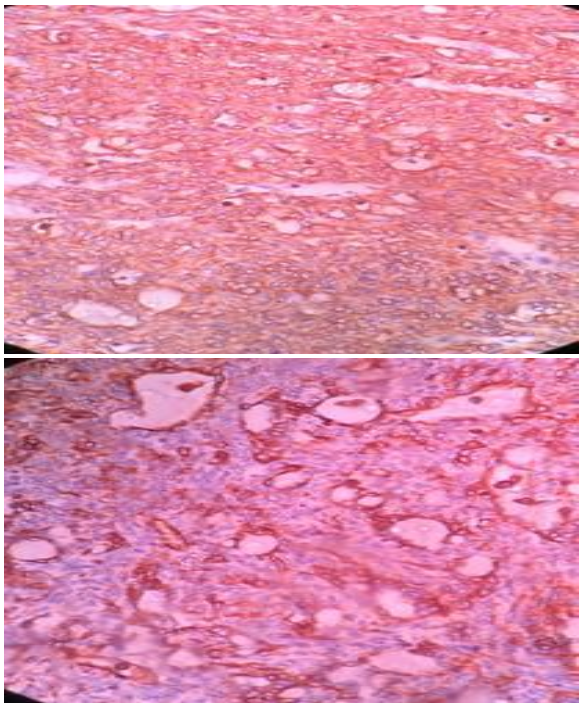
classical nested pattern as seen in all the cases with some showing spindle cell areas. One patient, young male of 21 years presented with a thyroid swelling, radiology and cytology findings suggested medullary carcinoma, but serum calcitonin levels were normal. Histopathology findings were also in favour of medullary carcinoma. IHC was done and was PCK and chromogranin positive and was confirmed as medullary carcinoma (**Figures - 9, 10, 11, 12**).

Figures – 14, 15: H&E sections (40X) (10X) diffuse sheets of spindle cells intermingled with tubules.



We also encountered one case each of rare variants like SETTLE, poorly differentiated carcinoma and NHL. A female patient aged 50 years who had thyroid swelling since 20 years, now presented with rapidly growing mass. Ultrasound revealed a malignant mass lesion in the inferior pole of left lobe extending into superior mediastinum and CT showed multiple thyroid nodules with malignant level 6 and 7 lymph nodes. Cytology revealed a cystic lesion in thyroid with possibility of metastasis in lymph node aspiration. Total thyroidectomy was done and revealed a mass in isthmus region measuring 4x3x2 cms with a grey-white lobulated cut surface (**Figure – 13**). Histopathology revealed a highly cellular neoplasm with lobulated growth pattern separated by variably thick septa. Lobules shows biphasic neoplasm consisting of fasicles of bland appearing spindle cells intermingled with epithelial component seen predominately as dilated tubules lined by flat epithelium and filled with acellular eosinophilic material (**Figures – 14, 15**). Spindle cell neoplasm with possibilities of SETTLE and ectopic thymoma was considered. IHC was done using the following markers PCK, vimentin, Tdt, CD5, TTF-1, and CD99. PCK, vimentin and CD99 were positive with CD5, Tdt and TTF being negative (**Figures - 16, 17, 18, 19**). It was diagnosed as SETTLE ruling out thymoma.

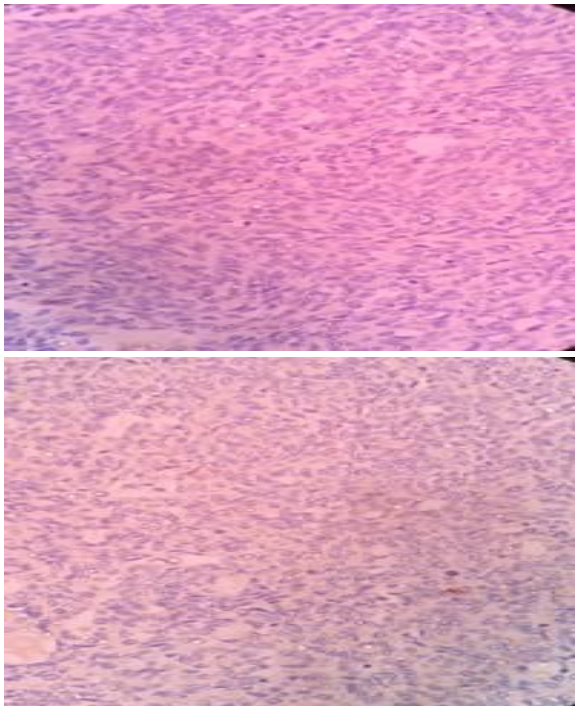
Figures – 16, 17: Positive IHC for PCK & vimentin. SETTLE.



The second case was female patient aged 48 years who had a previous history of papillary carcinoma thyroid and hemithyroidectomy was done, now presented with recurrent thyroid swelling and tracheal obstruction. Completion thyroidectomy was done with tracheal resection. Histopathology revealed a tumor arranged in nests and trabecular pattern, cells are small round to oval, with uniform, round hyperchromatic

nucleus, and scant to moderate vacolated eosinophlic cytoplasm (**Figures – 20, 21**). Follicular or papillary pattern was not seen. The tumor was seen invading the extrathyriodal tissue and trachea. Poorly differentiated carcinoma of thyroid was considered and was confirmed by IHC. CK7 was diffusely positive with TTF-1 and chromogranin being negative.

Figures – 18, 19: Negative IHC for Tdt & CD5.



NHL of thyroid gland was diagnosed in one female patient aged 50 years. She presented with rapidly growing thyroid mass and difficulty in swallowing. Ultrasonography revealed a malignant thyroid lesion with lymph nodal metastasis. Cytology was inconclusive. Total thyroidectomy was done and on cut section, revealed an ill-defined homogenous grey-white mass of 6x5x2 cm involving isthmus and left lobe of thyroid. Histopathology showed extensive involvement of thyroid with diffuse sheets of large lymphoid cells having finely dispersed chromatin and inconspicuous nucleolus and scant amount of cytoplasm (**Figure – 22**). Mitosis, foci of necrosis were also noted. Lymphoid follicles or hurthle cells were not seen. A diagnosis of primary lymphoma of thyroid favoring Non-Hodgkins lymphoma was considered and confirmed by immunohistochemistry. IHC showed positive staining with LCA, CD 20, and negative with TTF-1. Five lymph nodes were identified with reactive hyperplasia.

Figures – 20, 21: H&E sections (10X)(40X) showing trabaecular and insular pattern. Poorly differentiated carcinoma.

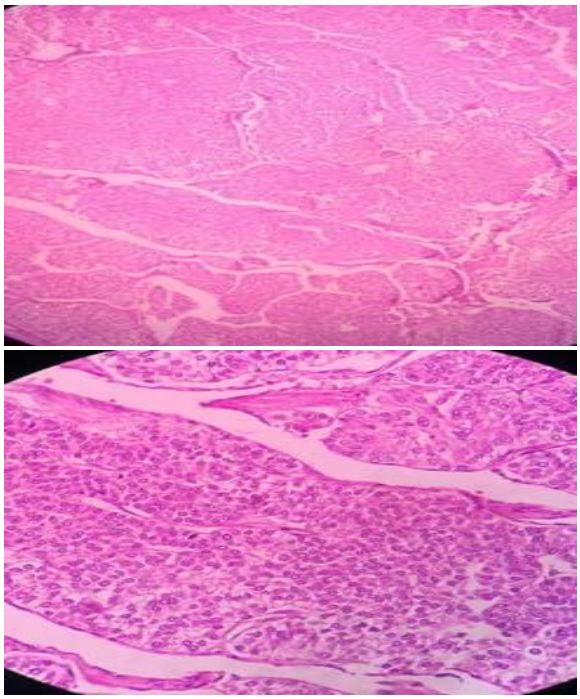
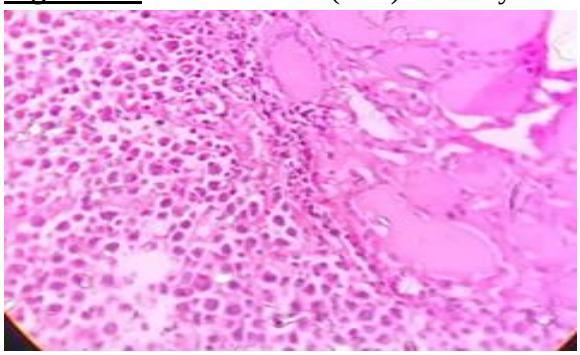


Figure - 22: H&E sections (10X) NHL thyroid.

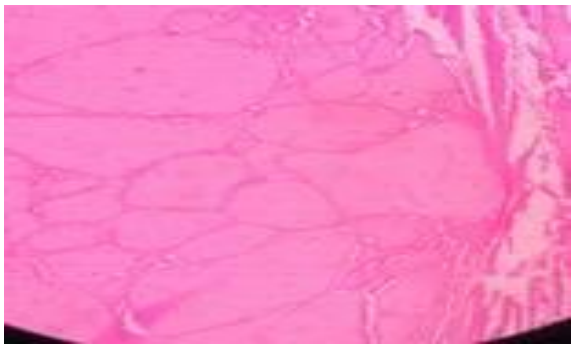


Discussion

Thyroid neoplasms are relatively rare comprising 3.9% of all tumors [1]. In the present study, papillary carcinoma thyroid is the most common neoplasm of all thyroid neoplasms accounting to 78.1% with female preponderance. Othman, et al. [2] and Gole, et al. [3] also observed the incidence of papillary carcinoma to be 76.6% and 78.56% respectively. It shows a wide age

range of 10-80 years, the youngest patient was a 10 year old girl. Radiation exposure and genetic factors are well known risk factors for papillary carcinoma. These tumors show an association with RET/PTC translocation, BRAF mutations [4].

Figure - 23: H&E sections (10X) macrofollicular adenoma.



Papillary carcinoma has a varied gross morphology, usually solid and cystic grey white in color with papillary projections. They can be unifocal or multi-focal. Most of papillary carcinomas shows papillary growth pattern but nuclear features are more important diagnostic hallmark. These include optically clear nuclei also known as "orphan annie" nuclei, nuclear grooves, intranuclear inclusions, and nuclear overcrowding. These features are enough to suggest papillary carcinoma even if the papillary pattern is absent in the tumor [5]. Chronic thyroiditis as well as follicular adenoma frequently shows similar intranuclear inclusions or nuclear grooves, but nuclear clearing may not be seen which should caution the pathologist in over diagnosing.

Many variants of papillary carcinoma exists associated with favourable or aggressive phenotype. In our study we had 16 cases of follicular variant of papillary carcinoma.The nuclei of this variant rarely have all of the features of papillary carcinoma. FVPTC is recognized by its follicular structure with papillary cytology, and composed of 2 subtypes; diffuse/invasive (infiltrative) and encapsulated type. FVPTC is associated with favorable prognosis especially if tumor is encapsulated [6]. Diffuse/invasive subtype has similar clinical features to usual papillary carcinoma.

We had case of FVPTC in a known case of NHL on treatment.The incidence of the concomitant thyroid carcinoma and hematological malignancy was 7% [7]. Several studies attempted to explain the link between thyroid carcinoma and extra-thyroid hematological malignancy implicating that "the long-term carcinogenic effects of specific cancer treatments might be responsible for a second cancer" [7, 8].

The association between thyroid cancer and other malignancies has been well documented in the literature [9]. We had a case of synchronous papillary carcinoma thyroid and parathyroid adenoma. Although several reports have been published regarding the coexistence of hyperparathyroidism and papillary thyroid carcinomas, concurrence of parathyroid adenoma and papillary thyroid carcinoma is extremely rare [10] and was first described in 1947 [11]. A low-dose radiation therapy for the head and neck, especially in childhood and adolescence, is known to induce thyroid and parathyroid tumors [12]. Preoperative biochemical studies, including serum calcium and iPTH concentrations, may be helpful to evaluate for occult primary hyperparathyroidism, and appropriate treatment for the parathyroid pathology including surgical resection can be performed.

The next common malignancy we encountered was anaplastic carcinoma accounting to 4.6% which was similar to other studies [13]. It usually affects elderly people, with a mean age of 65 years, and shows a female predominance. It is defined by the WHO as a highly malignant tumor wholly or partially composed of undifferentiated cells that retain features indicative of an epithelial origin, on immunohistochemical or ultrastructural ground [14]. Anaplastic carcinoma is a extremely invasive large solid tumor with necrosis and hemorrhage. Large, pleomorphic giant cells is one of hallmarks but may also be composed of spindle cells and squamoid cells. Primary or metastatic sarcoma, SETTLE, spindle

variant of medullary carcinoma forms the differential diagnosis mandating IHC studies. It stains positively with PCK, vimentin, and PAX8 and negative stainig is seen with TTF, chromogranin.

Medullary carcinomas had a similar incidence of 4.6% with a male preponderance, while the literature states that these tumors are more common in women when sporadic [15]. Only one study shows a similar picture correlating with our study [16]. 20-30% of medullary carcinomas are familial with autosomal dominant inheritance of germline RET mutations.medullary carcinoma shows a nodular growth pattern separated by fibro vascular bands, typical cells are oval to spindle with fine chromatin, inconspicuous nucleolus. Amyloid deposition is seen in in the stroma. It is uncommon for preoperative serum calcitonin to be in the normal reference range in patients with medullary carcinoma, and still had the presence of strong, diffuse immunohistochemical staining for calcitonin in the primary tumor [17]. These have been labeled "calcitonin-negative" or "non-secretory" medullary carcinoma. But we had a case with normal levels of serum calcitonin and demonstrating positive immunohistochemistry for chromogranin and calcitonin. Many studies have suggested poor prognosis of these calcitonin negative tumors. But, in the recent report of Frank-Raue, et al. [18], noted that, the stage and clinical course of calcitonin-negative medullary carcinomas were heterogeneous, and not necessarily associated with a poor prognosis.

Spindle epithelial tumor with thymus-like differentiation (SETTLE) is a very rare tumor of the thyroid believed to be derived from branchial pouch or thymic remnants and showing primitive thymic differentiation first characterized by Chan and Rosai [19]. SETTLE occurs in young patients, with indolent growth. A case of SETTLE was encountered in our study in an elderly female with long duration of thyroid swelling. In the literature, there are at least four other patients who had the thyroid mass noticed for four or more years, attesting to the generally slow growth of the neoplasm. Sometimes rapid enlargement of the lesion is noted in the long-standing thyroid mass as seen in our study [20]. It is composed of spindle cells of epithelial nature forming fascicles, merging into glandular structures taking the form of tubules, papillae, and cystic spaces.In SETTLE, immunohistochemical staining reveals positivity of the spindly tumor cells for epithelial markers and vimentin. So, SETTLE must be distinguished from sarcomatoid anaplastic carcinoma which has high mortality, the later has marked nuclear atypia and bizzare cells. IHC helps to distinguish it from Thymoma and spindle medullary carcinoma by negative staining with CD3, CD5, Tdt and chromogranin.

Poorly differentiated thyroid carcinoma is a rare and independent thyroid cancer histotype and was given its due recognition by treating it as separate entity in WHO 2004 classification [21]. It is defined as "a follicular-cell neoplasm that shows limited evidence of structural follicular cell differentiation and occupy both morphologically and behaviourally an intermediate position between differentiated (follicular and papillary carcinomas) and undifferentiated (anaplastic) carcinoma". We had case of poorly differentiated carcinoma in previously diagnosed known case of papillary carcinoma. The incidence is 1.19% which was low compared other studies [22]. These tumors are frequently invasive with increased incidence of distant metastasis and hence poor prognosis.

Primary thyroid lymphoma (PTL) is a rare cause of malignancy, accounting for < 5% of thyroid malignancies and < 2% of extranodal lymphomas [23]. In our study, one case of primary NHL of thyroid gland was encountered.Most thyroid lymphomas are non-Hodgkin's lymphomas (NHLs) of B-cell origin. Patients with Hashimoto's thyroiditis are at greater risk for developing primary lymphoma of thyroid gland. Although most thyroiditis cases do not proceed to lymphoma, most cases of lymphoma do arise in a background of thyroiditis.

Benign neoplasms accounted less with 6 cases (6.9%) of follicular adenoma. Most of them had normofollicular pattern and in one case macrofollicular (colloid) pattern was noted. This was different to study done by Ambreen Beigh, et al. [24]. The reason may be that our study was conducted at a cancer referral center.

Conclusion

We encountered a total of 87 cases of thyroid neoplasms including the rare variants, synchronous malignancies, second malignancies, SETTLE, poorly differentiated carcinoma. Papillary carcinoma was most commonly encountered thyroid malignancy followed by medullary and anaplastic carcinoma. Follicular adenoma was the commonest benign neoplasm. Multi-disciplinary approach is needed including clinical, radiological, morphological, and immunohistochemistry correlation for accurate diagnosis of rare variants.

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