DOI: 10.7860/NJLM/2021/45254:2453

Original Article

Pathology Section

Cyto-histomorphological Analysis of Thyroid Nodule

NAZIMA HAIDER[1], BALKUR KRISHNA MOORTHY ADIGA[2], RABAB NASIR MOHAMED BADRI[3], NIHAL MIRZA[4]

ABSTRACT

Introduction: Thyroid nodules are a very common medical condition worldwide with varied prevalence depending on population under study and diagnostic modality. They can be noticed by the patient as a swelling or by clinician as palpable nodule or using radiological technique such as Ultrasonography (USG) or Computerised Tomography (CT scan). Fine Needle Aspiration (FNA) is a very important modality to differentiate benign from malignant lesions. However, there are many diagnostic challenges, and in many instances, a definitive diagnosis is only possible through histopathology. In this study, clinico-cyto-histopathological analysis of thyroid nodules was made and discordant cases in cytology were analysed.

Aim: To study the cyto-histopathological analysis of thyroid nodules and to determine the accuracy of cytology to diagnose malignancy.

Materials and Methods: This was a three-year retrospective study of thyroidectomy specimens with cyto-histological correlation at Aseer Central Hospital, Abha, Saudi Arabia from January 2017 to December 2019. FNA was ultrasound-guided. Smears were fixed in 95% alcohol solution and Papanicolaou (PAP), Haematoxylin and Eosin (H and E) staining was done. The tissues were fixed in formalin, sampled and processed in automated tissue processing units. Immunohistochemistry was done wherever required using CytoKeratin (CK) 19, Calcitonin, CD34, Thyroid Transcription Factor 1 (TTF1), Ki67. Statistical analysis was done with IBM for the SPSS software version 25.0 for Windows.

Results: A total of 340 thyroidectomy specimens were received in three years. There were 265 females (78%) and 75 males (22%). Majority of patients (259 cases, 76.1%) were in 20 to 50 years of age. Colloid Goiter (CG) was the most common pathology (131 cases, 38.5%). Papillary Thyroid Carcinoma (PTC) was the most common malignancy with 98 cases (28.8%). Overall, Sensitivity of FNA in thyroid pathology in present study is 49.2%, Specificity is 84.2%, Positive Predictive Value (PPV) is 74.7%, Negative Predictive Value (NPV) is 63.5% and Diagnostic Accuracy (DA) of 67.2%.

Conclusion: The current study throws light on various thyroid lesions among thyroidectomy cases in mountain region of middle-east, along with cytological correlation. The study found the FNA as a great tool for preoperative categorisation of thyroid diseases, though the overall sensitivity was low with significantly high false negative rate. This study recommends better FNA techniques to avoid suboptimal material and better imaging modality and its interpretation for exact localisation of FNA site. It also highlights the higher incidence of incidental microcarcinoma in surgical specimens, warranting its significance on follow-up.

Keywords: Diagnostic errors, Fine needle aspiration, Malignant lesions

INTRODUCTION

Thyroid nodules are a very common medical condition, worldwide. Patients with deranged thyroid function, autoimmune thyroid disorders and the neoplastic enlargements may present with thyroid nodules. Prevalence of these nodules varies with population, geography, diagnostic modality, from 2-6% with palpation, 19-35% with ultrasound, and 8-65% in autopsy data. Incidence of nodules increases with age, in female population, people living in iodine deficient regions or having iodine deficient diet, and after radiation exposure [1]. Approach to preoperative diagnosis of thyroid nodules includes clinical, biochemical, radiological and cytological studies with the importance of excluding malignant nodules, which account for 4 to 6.5% of nodules and warrant early surgical management [2,3]. FNA is recommended for all nodules >1 cm with some exceptions [4]. Though FNA is considered very useful tool for separating malignant from benign cases, some preanalytical, analytical and postanalytical variables are likely to affect its interpretation and vary in different centers. False positive and negative results are attributed to many factors such as poor cellularity, preparation, fixation and staining artifacts producing cellular and architectural atypia and aspiration techniques. Newer and emerging entities in thyroid tumour nomenclature also throw light in explaining certain pitfalls of FNA. Tumours of uncertain malignant potential and follicular patterned lesions pose difficulty in interpretation by cytology. Challenge is also posed by Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS) for both cytopathologist and surgeon [5,6]. The current study involves an overview of thyroid nodules at tertiary healthcare center with emphasis on discordant cases in cytology by discussing the sources of false positive and negative cases.

MATERIALS AND METHODS

This was a three-year retrospective study of thyroid nodules from January 2017-December 2019 in Aseer Central Hospital (ACH), Abha, Saudi Arabia which is a tertiary hospital in the region of high mountains of Sarawat (maximum altitude 3200 meter above the sea level) near the Red Sea.

Inclusion criteria: All thyroidectomy specimens received in histopathology department during this time period were included in the study.

Exclusion criteria: Thyroid cases with only cytology without thyroidectomy were not included. Trucut biopsies were also not included in the study.

Clinical history, hormone status and cytology reports of these cases were retrieved from computer based patient record of the department and clinico-cyto-histological correlation was done where complete data was available. FNA was ultrasound-guided. Smears were fixed in 95% alcohol solution and PAP and

H and E staining done. The smears were evaluated according to the Bethesda system of thyroid cytology [5]. The tissues were fixed in formalin, sampled and processed in automated tissue processing units. Histopathological examination of the HandE stained sections was done. Immunohistochemistry was done wherever required with CK19 (for papillary carcinoma), Calcitonin (medullary carcinoma), CD34 (vascular invasion), TTF 1 and Ki67. Thyroid hormonal study (total and free thyroid hormones, TSH) was performed on serum specimens using automated immunoassays with UnicelDxI 600, Access Immunoassay System. Hormone status of patients with different thyroid pathologies was observed.

STATISTICAL ANALYSIS

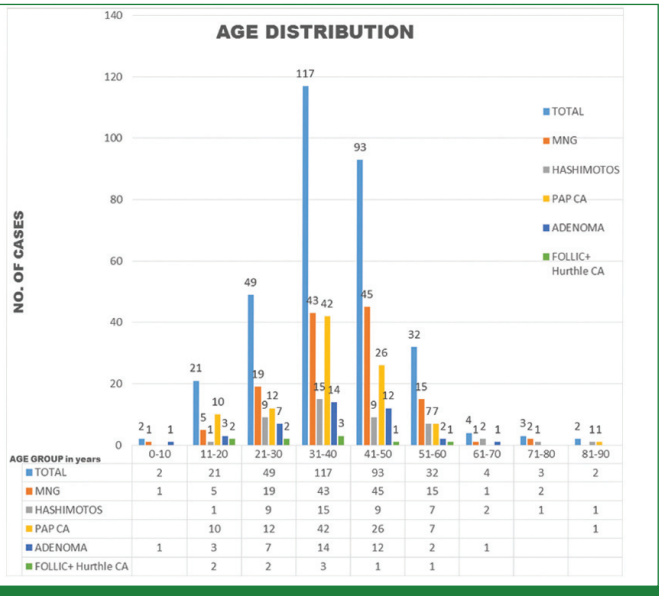
Statistical analysis was done with IBM SPSS statistics for Windows version 25.0, applying descriptive statistics.

RESULTS

Total of 340 thyroidectomy specimens were analysed [Table/Fig-1]. Female to male ratio of 3.5:1 was observed and majority of patients (259 cases, 76.1%) were in 20 to 50 years of age [Table/Fig-2]. CG was most common pathology where 124 presented as multinodular goiter (MNG) and 7 as solitary colloid nodule [Table/Fig-3]. Hormone status of most of the patients was euthyroid (105 cases, 80.1%). Only 14 cases (10.7%) were hypothyroid and 4 (3%) were hyperthyroid with

Histopathological diagnosis	Males	Females	No. of cases
Colloid Goiter	26 (19.8)	105 (80.1)	131 (38.5)
Hashimoto Thyroiditis	07 (15.6)	38 (84.4)	45 (13.2)
Granulomatous Thyroiditis	00	01 (100)	01 (0.3)
Follicular Adenoma	06 (21.4)	22 (78.6)	28 (8.2)
Hurthle cell Adenoma	04 (33.3)	08 (66.7)	12 (3.5)
Follicular tumour of Undetermined Malignant potential (FT-UMP)	03 (50)	03 (50)	06 (1.8)
Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)	01 (25)	03 (75)	04 (1.2)
Papillary carcinoma	23 (23.4)	75 (76.6)	98 (28.8)
Follicular carcinoma	01 (16.7)	05 (83.3)	06 (1.8)
Hurthle cell carcinoma	01 (33.3)	02 (66.7)	03 (0.9)
Medullary carcinoma	02 (100)	00	02 (0.6)
Poorly differentiated/Anaplastic carcinoma	01 (50)	01 (50)	02 (0.6)
Lymphoma	00	02 (100)	02 (0.6)
Total	75 (22)	265 (78)	340 (100)

[Table/Fig-1]: Histopathological diagnosis of thyroid nodules.



[Table/Fig-2]: Age distribution of thyroid lesions.

Thyroid swelling	Solitary nodule	Multinodular	Diffuse	Total
Goiter	7 (5.3)	124 (94.6)		131 (38.5)
Thyroiditis	1 (2.1)	29 (63)	16 (34.8)	46 (13.5)
Adenoma	14 (35)	26 (65)		40 (11.8)
FT-UMP	04 (66.6)	01 (16.6)	01 (16.6)	06 (1.8)
NIFTP		03 (75)	01 (25)	04 (1.2)
Papillary carcinoma	09 (9.2)	47 (47.9)	42 (42.9)	98 (28.8)
Follicular and Hurhtle cell carcinoma	6 (66.7)	3 (33.3)		09 (2.6)
Medullary carcinoma	2 (100)			02 (0.6)
Poorly differentiated carcinoma	2 (100)			02 (0.6)
Lymphoma			2	02 (0.6)
Total	45 (13.2)	233 (68.5)	62 (18.2)	340 (100)

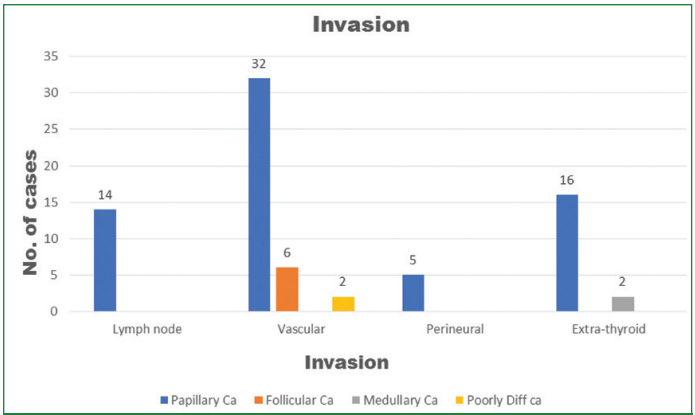
[Table/Fig-3]: Type of thyroid swelling with diagnosis.
FT-UMP: Follicular tumour of uncertain malignant potential; NIFTP: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features

toxic changes. In eight cases, hormone status was not determined. 87 cases (25.6%) showed hyperplastic epithelium along with papillary hyperplasia and hyperplastic adenomatous nodules.

Hashimoto Thyroiditis (HT) was the second most common lesion affecting mainly women of 3rd to 5th decades. Though, the majority (55.6%) was hypothyroid, significant (44.4%) were euthyroid [Table/Fig-1-3]. Histologically, 35 cases (77.8%) showed Hurthle cell changes and 22 cases (48.9%) revealed atrophic or destructed follicles. There were 40 cases (11.8%) of thyroid adenoma with 28 cases of Follicular Adenoma (FA) and 12 cases of Hurthle cell adenoma between 30 to 50 years. Some presented as dominant nodule in MNG (26 cases) while others as solitary nodule (14 cases). Nine cases showed lymphocytic/ HT in rest of the thyroid tissue. Majority (27 cases) were euthyroid, 10 presented with hypothyroidism and three showed hyperthyroidism. Six cases were reported as Follicular Tumour of Uncertain Malignant Potential (FT-UMP) with presence of questionable capsular/vascular invasion and four cases showed foci of Non-invasive Follicular Thyroid Neoplasm with Papillary (NIFTP)-like nuclear features. Half of the cases were associated with HT and half with MNG with hyperplasia. CK 19 and CD 34 (for vascular invasion) were used as immunological markSers in these borderline cases. Three cases with foci of NIFTP were positive for CK19.

PTC was the most common malignancy with 98 cases (28.8%), mainly in women (75, 76.6%) with mean age 36±10.5 years. Youngest patient was 14 years and oldest was 90 years female [Table/Fig-1,2]. Majority (50 cases, 51%) were associated with HT while 34 cases (34.6%) with MNG. About 1/5 cases revealed Hurthle cell changes in surrounding thyroid tissue. Histologically, classical type comprised around 1/3 of cases (35, 35.7%) and follicular (10.2%) and oncocytic (9.1%) variants were relatively common. Rare variants like sclerosing (4 cases, 4.1%), encapsulated (2 cases, 2%) and tall cell (1 case, 1%) were noted. But the majority (37 cases, 37.7%) were microscopic foci (less than 1 mm) found incidentally with other conditions namely HT (18 cases), MNG (15 cases), follicular adenoma (four cases) and all of them were CK 19 positive. Psammomatous calcification was present in 42 cases (42.8%). Three cases had metaplastic bone formation. PTC cases showing invasion are depicted in [Table/Fig-4]. There were six cases of follicular carcinoma and three cases of Hurthle cell carcinoma. Mean age was 30±11.3 years. Six cases (66.7%) showed vascular invasion [Table/Fig-1-4]. One case (53-year-old male) of poorly differentiated carcinoma showed insular pattern (50-60% TTF1 positive) while other (68-year-old female) was anaplastic carcinoma, 25% TTF1 positive.

FNA was performed in 303 cases, out of which 32 were unsatisfactory/ nondiagnostic cases. Therefore, cyto-histo correlation was possible



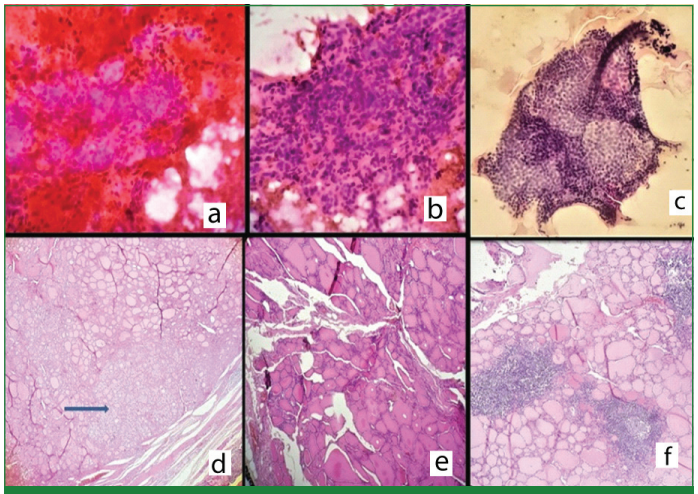
[Table/Fig-4]: Invasion by malignant thyroid tumours.

in 271 cases [Table/Fig-5]. FNA diagnosis was done on Bethesda system for thyroid cytology [7]. A total of 168 cases were reported as Benign Follicular Nodule (BFN)/Benign Colloid Nodule (BCN), out of which 105 were correctly correlated on histopathology as CG (True Negative, TN). Remaining 63 cases were benign or malignant conditions on histology which included 22 cases of FA, 23 cases of PTC out of which 20 were micropapillary carcinoma, 3 cases of follicular carcinoma, 12 cases of HT, 1 case of NIFTP and 2 cases of FT-UMP. (False Negative, FN). Twelve cases of thyroiditis on FNA were correctly correlated on histology as HT (TN). Nineteen cases were reported on FNA as Atypia of Undetermined Significance (AUS)/Follicular Lesion of Undetermined Significance (FLUS) which were related on histology as Hurthle cell adenoma (three cases), FA (two cases) and NIFTP, FT-UMP (one case each). (True Positive, TP). Remaining were MNG (five cases), HT (three cases) (False Positive, FP) and PTC (four cases) on hisology (FN). Twenty-four cases were Suspicious for Follicular/Hurthle cell neoplasmon FNA out of which 18 turned out be benign or malignant follicular neoplasms (TP). Remaining six cases were non-neoplastic lesions on biopsy, HT (four cases) and MNG with nodular hyperplasia (two cases). Out of 24 suspicious cases for Papillary carcinoma on FNA, 16 were diagnosed the same on histology (TP). Rest eight cases were non-neoplastic and benign follicular conditions which included three cases of HT, two each of NIFTP and MNG and one case of FA (FP).

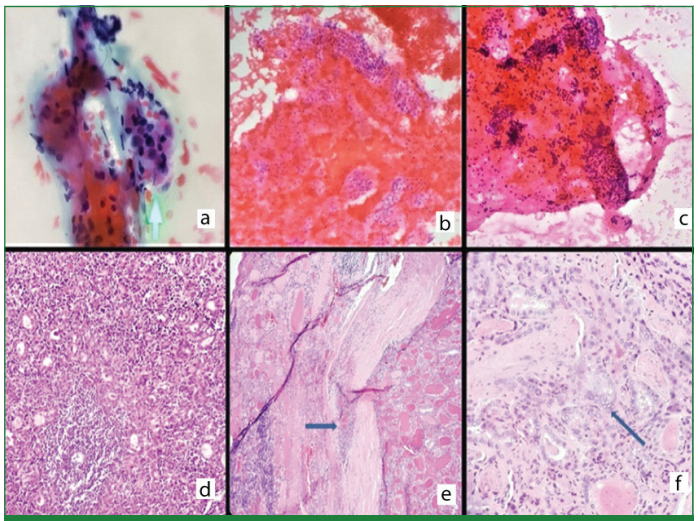
Cyto diagnosis	Histodiagnosis					Total
	Colloid nodule/ Nodular Goiter	Thy-roiditis	Benign tumour	Border-line*	Malignant	
Non-diagnostic/ Unsatisfactory	21	5	2	-	4	32 (10.6)
Benign	105	24	22	3	26	180 (59.4)
Atypia of Undetermined Significance (AUS)	5	3	5	2	4	19 (6.3)
Suspicious for Follicular Neoplasm	2	4	9	2	7	24 (7.9)
Suspicious for malignancy (PTC)	2	3	1	2	16	24 (7.9)
Malignant	-	-	-	-	24	24 (7.9)
Total	135	39	39	9	81	303 (100)

[Table/Fig-5]: Cyto-histological correlation of thyroid lesions.
Borderline* here includes other encapsulated follicular patterned thyroid tumours; PTC: Papillary thyroid carcinoma

Eighteen cases of malignant papillary carcinoma on FNA and two cases each of anaplastic carcinoma, medullary carcinoma and lymphoma were correctly correlated. (TP) Images of some cases where cytological and histopathological diagnosis were discordant are shown in [Table/Fig-6,7]. Therefore, overall Sensitivity of FNA in thyroid pathology in present study is 49.2%, Specificity is 84.2%, PPV is 74.7%, NPV is 63.5% and DA of 67.2% with a concordance rate of 67.2% and discordance rate of 32.8% [Table/Fig-8].



[Table/Fig-6]: a) Blood stained smear showing groups of atypical cells with nuclear enlargement, overlapping and irregularity. Suspicious for papillary carcinoma, (Bethesda IV). H&E, 200x; b) Smear showing sheet of follicular cells exhibiting slightly pleomorphic and mildly enlarged nuclei along with many small groups of bland looking follicular cells. Atypical cells of undetermined significance (AUS), (Bethesda III). H&E, 200x; c) Smear showing nests and sheets of hypercellular follicular cells, suspicious for follicular neoplasm, (Bethesda IV), H&E, 200x; d) Follicular adenoma (Hurthle cell type); Encapsulated follicular neoplasm with many cells showing oncocytic/hurthle cell changes (arrow) H&E, 200x; e) Multinodular colloid goiter. Dilated follicles lined by flattened to cuboidal epithelium in variable sized nodules. H&E, 200x; f) Multinodular colloid goiter with background of Hashimoto thyroiditis H&E, 200x.



[Table/Fig-7]: a) Smear showing scattered atypical degenerated cells of undetermined significance (arrow). (Bethesda III). PAP, 200x; b) Blood stained smear showing benign follicular cells, (Bethesda II). H&E, 200x; c) Hypocellular blood stained smear with benign follicular cells and thin colloid in background, (Bethesda II) H&E, 100x; d) Hashimoto thyroiditis. Dense lymphoplasmacytic infiltration with severe damage of thyroid follicles which are lined by Hurthle cells. H&E, 400x; e) Follicular carcinoma. Colloid filled macro and microfollicles with complete capsular invasion (arrow). H&E, 100x; f) Papillary carcinoma in a background of goitrous colloid nodule. Tumour composed of papillary structures lined by malignant cells with nuclear clearing, enlargement and overlapping (arrow) H&E, 200x.

Studies	Sensitivity	Specificity	NPV	PPV	DA
Present study	49.2%	84.2%	63.5%	74.7%	67.2%
Chao TC et al., [37]	86.1%	59.7%	94.9%	33%	64.6%
Bukhari MH et al., [35]	90%	87.5%	79.5%	93%	87%
Upadhyaya P et al., [28]	75%	100%	92%	100%	93.57%
Sharma C [38]	89.5%	98%	98.6%	84.6%	97%
Nandedkar SS et al., [39]	85.7%	98.6%	98%	90%	97.1%
Handa U et al., [36]	97%	100%	100%	96%	98.4%

[Table/Fig-8]: Comparison with past studies [28, 35-39].

DISCUSSION

Thyroid enlargement or goiter is a very common manifestation of thyroid pathology manifested in 5-8% of population with varied pathogenesis which includes non-neoplastic, inflammatory, benign and malignant diseases of thyroid [8]. It may be diffuse, solitary, nodular or multi-nodular enlargement which is easily accessible for clinical examination. USG followed by Fine needle Aspiration Cytology (FNAC) along with hormone assay is usual clinical approach for diagnosis. Complications of surgery along with lifetime risk of hypothyroidism and hypoparathyroidism due to removal of the glands can be avoided by following correct approach for diagnosis. Surgery is mainly done for malignancies although signs of compression and toxicity may be the other indications [9]. In a study from Western Saudi Arabia, out of 845 cases of thyroidectomy from 1997 to 2008, the non-neoplastic group included MNG (311 cases; 36.8%), HT/chronic lymphocytic thyroiditis (64 cases; 7.6%), single hyperplastic nodule (51 cases; 6%), Grave's disease (8 cases; 0.9%), miscellaneous (58 cases; 6.9%) [10]. In another study from Yemen, 667 thyroidectomies from 1997 to 2001 were MNG (62.8%), thyroiditis (5.6%), Graves (2%) and FA (11.8%). While a study from Pakistan with 624 cases, there were 76% MNG, thyroiditis (2.1%), CG, toxic goiter, tuberculosis (0.3%) each [11,12].

Prevalence of goiter is high in our region (13-30%) and Iodine Deficiency Disorders (IDD) are endemic [13]. Total goiter prevalence varies from one region to another worldwide from 4.7% in America to 28.3% in Africa with average of 15.8% [14]. The current study showed 105 cases of euthyroid goiter i.e., 30.9% of all thyroidectomy cases, which may be due to iodine deficiency attributed to high altitude.

HT/thyroiditis is found to be more frequent than expected when diagnosed by cytology as patients progress from euthyroid stage to full blown hypothyroid stage. There are conflicting reports of FNA accuracy of HT with higher rate of FN and FP results due to hyperplastic follicular/Hurthle cells, enlarged and irregular nuclei in many cases [15]. Missing HT in cytology reports in this study is mainly because of paucity of lymphocytes due to patchy inflammatory involvement of the gland and FNA was done from area suspicious for malignancy. Atypical cytology was due to atypical Hurthle cells and atrophic thyroid follicular cells. Other studies have similar observations with cytomorphological features of HT resembling lesions like MNG with degenerative changes, reactive lymphnode, follicular or Hurthle cell neoplasm, papillary carcinoma and lymphoma [16,17]. In this study, 50 (51%) out of 98 cases of PTC were associated with HT. Fifteen cases of micropapillary carcinoma were incidentally found with HT. Nine cases of FA and two cases of NIFTP also showed association with HT. Studies have shown increased risk of thyroid malignancy due to chronic inflammatory process of HT with highest association with papillary carcinoma [16].

Non-invasive, encapsulated tumour composed exclusively of follicles which are lined by cells having nuclear features associated with PTC but without any other malignant features are designated as NIFTP [18,19]. Another borderline/grey zone lesion is FA with doubtful capsular penetration called FT-UMP [20]. Cyto-histological correlation studies of NIFTP have shown cells arranged in microfollicles with focal nuclear features of PTC, making it difficult to distinguish from invasive encapsulated follicular variant of PTC on FNA as capsule can't be evaluated. Many cases have been reported as follicular neoplasm/suspicious for follicular neoplasm, AUS/FLUS and suspicious for malignancy resulting in a FP analysis oncytology [6,21]. In present study, four cases of NIFTP were reported on cytology as BCN/BFN (one case), AUS/FLUS (one case), suspicious for PTC (two cases). While five out of six cases of FT-UMP were reported as BCN/BFN (two cases), AUS/FLUS (one case), suspicious for follicular neoplasm (two cases). These indeterminate lesions are therefore difficult to interpret and correlate, both on histology and cytology.

AUS/FLUS category in cytology which includes architectural atypia not sufficient to be classified as suspicious for neoplasm or malignancy but more marked than benign should be used carefully. It should be limited to 7% [7]. It is 6.3% in present study [Table/Fig-5]. Preparation, fixation and staining artifacts of FNA slides hamper evaluation of cellular details and may produce artificial cellular atypia which may be interpreted as AUS/FLUS. Similarly, improper aspiration techniques may produce blood stained or poor cellularity smears with atypical cells. Presence of oncocytic cells, occasional microfollicles, also produces difficulty in interpretation in such cases. These issues therefore also increase chances of FP cases on FNA. AUS/FLUS category therefore poses a challenge for both cytopathologist in interpretation and surgeon in management. Re-aspiration is advised in many cases after clinical and radiological correlation [6].

Reporting of follicular neoplasms on FNA is also challenging which are identified by the cytological criteria of high cellularity, abundant microfollicles, lack of colloid and macrophages. Histologically, follicular pattern is seen in hyperplastic nodules, adenomatoid nodules, FA and malignant neoplasms like follicular carcinoma, follicular variant of PTC. But, most challenging are borderline or indeterminate lesions [18]. Trapped follicles in fibrosis of hyperplastic nodules arise suspicion of capsular invasion. However, capsular invasion cannot be commented on cytology [20]. Limited cellularity smears, presence of more number of macrofollicles over microfollicles and not identifying these microfollicles leads to underdiagnosis as benign nodules [22]. Twenty-two cases of FA and three cases of follicular carcinoma were reported as BFN/BCN in present study [Table/Fig-5].

Thyroid cancers are found in 5-10% of thyroid nodules [23]. They are second most common among Saudi female population after breast cancer, accounting for 11% of all newly diagnosed cancers and 14th among males [24]. Improved diagnostic techniques, obesity, diabetes, autoimmune thyroiditis, smoking prevalence, iodine deficiency and genetics have been attributed to this rise in thyroid cancer cases [25]. PTC accounts for 70-90% of all differentiated malignancies of thyroid with mean age of 45 years [26]. In present study, PTC accounted for 86.7% (98 out of 113 malignant tumours) of all malignancies [Table/Fig-1]. It is diagnosed by the characteristic nuclear features with nucleomegaly, intranuclear groves, pseudoinclusions, nuclear overlapping and most important nuclear clearing ("Orphan Annie cells"). A 50% are conventional/classical PTC and 50% also reveal "Psamomma bodies" [27]. Increased cellularity, large sheets of follicular cells with round nucleus, pale chromatin, and occasional nuclear grooving in MNG and cases of HT with focal pale powdery chromatin, occasional nuclear inclusion, and intranuclear grooving can mislead to diagnosis of PTC on FNA. In this study, three cases were finally diagnosed as HT, one as FA and two as NIFTP and MNG each, which were reported as suspicious for malignancy (PTC) on FNA [Table/Fig-5,6a,b]. On the other hand, follicular cells with pale nuclei with occasional nuclear grooving and absence of intranuclear inclusion were considered as a part of cystic degeneration in CG and not as PTC, thereby leading to an underdiagnosis [28]. Here, 23 cases of PTC were reported as BFN/BCN on FNA, but 20 were micropapillary variant.

Studies have shown incidence of medullary carcinoma to be 0.5-5%, anaplastic carcinoma to be 0.5-2% and lymphoma to be 1-2% of thyroid malignancies [1]. If unequivocal cellular features are present, these rare malignancies can be interpreted accurately on FNA. There is a high specificity in diagnosing these malignant lesions as seen in present study also [28-31]. Thyroid malignancies have been

shown to be associated with MNG and HT. The exact pathogenesis of malignancy in MNG is not clear but risk cannot be underestimated and any dominant nodule in MNG should be carefully evaluated. HT being a chronic inflammatory disease and well-known cause-effect relationship between chronic inflammation and malignancy is postulated as a reason for increased association between HT and papillary carcinoma [16,32,33]. Immunohistochemistry is needed in equivocal cases which include TTF1, Hector Battifora Mesothelial-1 (HBME-1), Galectin-3, and CK19, calcitonin. TTF1 expression is seen in 25-90% of poorly differentiated/undifferentiated and medullary carcinomas. HBME-1, Galectin-3 and CK-19 are used in combination to differentiate papillary carcinoma and its follicular variant from benign lesions [34].

Differences in sensitivity, specificity and DA have been reported in different studies [Table/Fig-8] [28,35-39]. Sensitivity in present study is lower with a high FN rate. The reasons seem to be diluted, low cellularity samples, and sampling error due to the aspiration from large benign lesion with adjacent malignant lesions missed. Also, sampling was done by different operators including junior doctors. Difficulty in distinguishing between benign and low-grade malignant lesions also increases FN reports. Most studies have FN rate between 1 to 11% and FP rate of 0-9% [40,41], but present study have 22% and 7.2%, respectively. However, some other studies that have also shown very high FN rate with similar observations [42,43].

Limitation(s)

This is a retrospective, institutional based study of thyroidectomy specimen. The study did not include the assessment of FNA techniques, cytohistochemistry and cytogenetics, which could have given further insight for accurate diagnosis. Follicular tumours per se are another limitation in FNA as capsular and vascular invasion cannot be commented.

CONCLUSION(S)

FNA is a great tool for preoperative categorisation of thyroid diseases, though further improvement in technique and overall updating of histopathological knowledge of emerging thyroid entities are recommended for the better interpretation and accuracy of cytological smears. Study also highlights high incidence of incidental microcarcinoma in surgical specimens responsible for FN rate in FNA, though its clinical significance needs to be followed-up. Follicular lesions also pose difficulty in FNA interpretation.

REFERENCES

[1] Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clin Endocrinol Metab. 2008;22(6):901-11.
[2] Werk EEJr, Vernon BM, Gonzalez JJ, Ungaro PC, McCoy RC. Cancer in thyroid nodules. A community hospital survey. Arch Intern Med. 1984;144(3):474-76.
[3] Lin JD, Chao TC, Huang BY, Chen ST, Chang HY, Hsueh C. Thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine-needle aspiration cytology. Thyroid. 2005;15(7):708-17.
[4] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):01-133.
[5] Rossi ED, Adeniran AJ, Faquin WC. Pitfalls in thyroid cytopathology. Surg Pathol Clin. 2019;12(4):865-81.
[6] Bongiovanni M, Bellevicine C, Troncone G, Sykiotis GP. Approach to cytological indeterminate thyroid nodules. Gland Surg. 2019;8(2):S98-104.
[7] Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid. 2017;27(11):1341-46.
[8] Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214.
[9] Kostoglou-Athanassiou I. Indications for surgical treatment in benign thyroid disease. Hellenic J Surg. 2015;87:18-23.
[10] Salama S, Al-Qahtani M, Al- Maghrabi J, Abdullah LS. Histopathological pattern of thyroid lesions in western region of Saudi Arabia. New EgyptJ Med. 2009;40(6):580-85.
[11] Al-Hureibi KA, Abdulmughni YA, Al- Hureibi MA, Al- Hureibi YA, Ghafoor MA. The epidemiology, pathology, and management of goitre in Yemen. Ann Saudi Med. 2004;24(2):119-123.
[12] Qureshi IA, Khabaz MN, Baig M, Begum B, Abdelrehaman AS, Hussain MB. Histopathological findings in goiter: A review of 624 thyroidectomies. Neuroendocrinol Lett. 2015;36(1):48-52.
[13] Abbag FI, Abu-Eshy SA, Mahfouz AA, Al-Fifi SA, El-Wadie H, Abdallah SM, et al. Iodine-deficiency disorders in the Aseer region, south-western Saudi Arabia: 20 years after the national survey and universal salt iodization. Public Health Nutrition. 2015;18(14):2523-29.
[14] Andersson M, Takkouche B, Egli I, Allen HE, de Benoist B. Iodine status worldwide, WHO global database on iodine deficiency: Department of Nutrition for Health and Nutrition. Geneva: World Health Organization; 2004.
[15] Kapan M, Onder A, Girgin S, Ulger BV, Firat U, et al. The reliability of fine-needle aspiration biopsy in terms of malignancy in patients with Hashimoto thyroiditis. Int Surg. 2015;100(2):249-53.
[16] Morais SN, Stuart J, Guan H, Wang Z, Cibas ES, Frates MC, et al. The impact of Hashimoto's thyroiditis on thyroid nodule cytology and risk of thyroid cancer. J Endocr Soc. 2011;3(1):791-800.
[17] Gayathri B, Kalyani R, Harendra KM, Krishna PK. Fine needle aspiration cytology of Hashimoto's thyroiditis- A diagnostic pitfall with review of literature. J Cytol. 2011;28(4):210-13.
[18] Suster S. Controversies regarding the interpretation of follicular thyroid nodules. Arch Pathol Lab Med. 2019;143(12):1472-76.
[19] Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LDR, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: A paradigm shift to reduce overtreatment of indolent tumours. JAMA Oncol. 2016;2(8):1023-29.
[20] Sukumaran R, Kattoor J, Pillai KR, Ramadas PT, Nayak N, Somanathan T, et al. Fine Needle Aspiration cytology of thyroid lesions and its correlation with histopathology in a series of 248 patients. Indian J Surg Oncol. 2014;5(3):237-41.
[21] Maletta F, Massa F, Torregrossa L, Duregon E, Casadei GP, Basolo F, et al. Cytological features of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. Hum Pathol. 2016;54:134-42.
[22] Yoo C, Choi HJ, Im S, Jung JH, Min K, Kang CS, et al. Fine needle aspiration cytology of thyroid follicular neoplasm: Cytohistologic correlation and accuracy. Korean J Pathol. 2013;47(1):61-66.
[23] Dean DS, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. Cancer Control. 2000;7(3):229-39.
[24] Kingdom of Saudi Arabia, Ministry of Health, National Cancer Registry. Cancer Incidence Report. 2004;1999-2000.
[25] Aljabri KS, Bokhari SA, Al Shareef MA, Khan PM. An 18-year study of thyroid carcinoma in the western region of Saudi Arabia: A retrospective single-center study in a community hospital. Ann Saudi Med. 2018;38(5):336-43.
[26] Baloch ZW, LiVolsi VA. Pathology of thyroid gland In: VA LiVolsi, SL Asa (eds), Endocrine Pathology. Churchill Livingstone, New York 2002; pp. 61-101.
[27] Sak SD. Variants of papillary thyroid carcinoma: Multiple faces of a familiar tumor. Turk Patoloji Derg. 2015;31(Suppl 1):34-47.
[28] Upadhyaya P, Dhakal S, Adhikari P, Adhikari B, Khadka D, Niraula RS. Histopathological review of diagnostic categories of the bethesda system for reporting thyroid cytopathology – An institutional experience of 5 years. J Cytol. 2019;36(1):48-52.
[29] Yang J, Schnadig V, Logrono R, Wassrman PG. Fine-needle aspiration of thyroid nodules: A study of 4703 patients with histologic and clinical correlations. Cancer. 2007;111(5):306-15.
[30] Ahmed M, Al-Saihati B, Greer W, Al-Nuaim A, Bakheet S, Abdulkareem AM, et al. A study of 875 cases of thyroid cancer observed over a fifteen-year period (1975-1989) at the King Faisal Specialist Hospital and Research Centre. Ann Saudi Med. 1995;15(6):579-84.
[31] Alzahrani AS, Alomar H, Alzahrani N. Thyroid cancer in Saudi Arabia: A histopathological and outcome study. Int J Endocrinol. 2017;2017:8423147.
[32] Gandolfi PP, Frisina A, Raffa M, Renda F, Rocchetti O, Ruggeri C, et al. The incidence of thyroid carcinoma in multinodular goiter: Retrospective analysis. Acta Biomed. 2004;75(2):114-17.
[33] Luo J, McManus C, Chen H, Sippel RS. Are there predictors of malignancy in patients with multinodular goiter? J Surg Res. 2012;174(2):207-10.
[34] Liu H, Lin F. Application of immunohistochemistry in thyroid pathology. Arch Pathol Lab Med. 2015;139(1):67-82.
[35] Bukhari MH, Niazi S, Hanif G, Quershi SS, Munir M, Hasan M, et al. An updated audit of fine needle aspiration cytology procedure of solitary thyroid nodule. Diagn Cytopathol. 2008;36(2):104-12.
[36] Handa U, Garg S, Mohan H, Nagarkar N. Role of fine needle aspiration cytology in diagnosis and management of thyroid lesions: A study of 434 patients. J Cytol. 2008;25:13-17.
[37] Chao TC, Lin JD, Chao HH, Hsueh C, Chen MF. Surgical treatment of solitary thyroid nodules via fine-needle aspiration biopsy and frozen-section analysis. Ann Surg Oncol. 2007;14(2):712-18.
[38] Sharma C. Diagnostic accuracy of fine needle aspiration cytology of thyroid and evaluation of discordant cases. J Egypt Natl Canc Inst. 2015;27(3):147-53.
[39] Nandedkar SS, Dixit M, Malukani K, Varma AV, Gambhi S. Evaluation of thyroid lesions by fine-needle aspiration cytology according to bethesda system and its histopathological correlation. Int J App Basic Med Res. 2018;8(2):76-82.
[40] Flanagan MB, Ohori NP, Carty SE, Hunt JL. Repeat thyroid nodule fine-needle aspiration in patients with initial benign cytologic results. Am J Clin Pathol. 2006;125(5):698-702.

[41] Tee YY, Lowe AJ, Brand CA, Judson RT. Fine-needle aspiration may miss a third of all malignancy in palpable thyroid nodules: A comprehensive literature review. Ann Surg. 2007;246(5):714-20.
[42] Mistry SJ, Mani N, Murthy P. Investigating the value of fine needle aspiration cytology in thyroid cancer. J Cytol. 2011;28(4):185-90.
[43] Richmond BK, Rudy J, Benny C, Adam U, Zachary AR, William M, et al. False-negative results with the Bethesda system of reporting thyroid cytopathology: Predictors of malignancy in thyroid nodules classified as benign by cytopathologic evaluation. Am Surg. 2014;80(8):811-16.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, King Khalid University, Abha, Aseer, Saudi Arabia.
2. Professor, Department of Pathology, King Khalid University, Abha, Aseer, Saudi Arabia.
3. Consultant, Department of Histopathology, Aseer Central hospital, Abha, Aseer, Saudi Arabia.
4. Specialist, Department of Histopathology, Aseer Central hospital, Abha, Aseer, Saudi Arabia.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Nazima Haider,
Assistant Professor, Department of Pathology, College of Medicine, King Khalid University, Abha, Aseer, Saudi Arabia.
E-mail: nazima_haider@yahoo.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 04, 2020
- Manual Googling: Oct 14, 2020
- iThenticate Software: Dec 28, 2020 (11%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 04, 2020**
Date of Peer Review: **Jul 22, 2020**
Date of Acceptance: **Oct 16, 2020**
Date of Publishing: **Jan 01, 2021**