ORIGINAL RESEARCH

Fine Needle Aspiration of Goiter (Benign and Non-Neoplastic) with Thyroid Function Abnormalities

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ABSTRACT

Introduction: A thyroid nodule is the prime indication for FNA, which is also a cheap and effective investigation. The current study seeks an association between benign goiter and aberrant thyroid function tests. Can thyroid FNA anticipate overt morbidity resulting from thyroid function abnormalities? **Materials and methods:** FNA records of 173 patients were studied along with thyroid function test(TFT) results. Slide review was undertaken where FNA impression did not correspond to the TFT. **Results:**The female: male ratio was 149:24. Two(1.15%) had inadequate cellularity. 95/173 cases had abnormal TFTs. Multinodulargoiter(126), Hashimoto thyroiditis(43) and two and one case of granulomatous and unclassified thyroiditis respectively constituted our diagnostic profile. Abnormalities in TFT did not correlate with age group, gender or FNA diagnoses. However, hypothyroidism (clinical and subclinical) was significantly observed in Hashimoto thyroiditis(HT) cases. Again, scant colloid and cell change significantly correlated with HT. The histological correlation was obtained in 46 cases. Four neoplastic cases were seen, among which there were three papillary carcinomas focally arising within cysts. **Conclusions:** The major observation in this study is the subset of euthyroid and subclinically hypothyroid cases (23/43, 53.48%) of Hashimoto thyroiditis ($p = 0.0021$). If treated with thyroxine replacement, overt hypothyroidism, particularly in pregnant women who are at risk of developing antithyroid antibodies, may be prevented. In addition, inadequacy rate (1.15%) in the current study is low. False negatives 3/46(6.5%), though available on a meager and selected subset of the patient population is still within the range of published data.

KEYWORDS: Fine-needle aspiration, goiter, Hashimoto thyroiditis, Multinodular goiter, Hyperthyroidism

INTRODUCTION

Thyroid nodule (TN) remains the main indication of thyroid FNA, the aim being to distinguish neoplastic from the non-neoplastic lesions and thereby reduce the number of diagnostic surgeries.[1] A goiter or thyroid nodule may accompany thyroid function abnormalities and/or antithyroid antibodies. Though these conditions may be investigated by ultrasonogram scans, radioactive iodine uptake and radionuclide scans and serum thyroid antibody tests, they are all costly to the Indian population except perhaps the plain ultrasonogram, and thus FNA offers itself as a cheap, affordable and reliable diagnostic modality to an overwhelming majority of the patients. We have attempted to seek out whether any real associations between benign goiter and thyroid function abnormalities exist. By performing the FNA, a minimally invasive procedure and attempting to diagnose the condition by relating to the thyroid function tests(TFT), can we forestall substantial morbidity in some patients?

MATERIALS AND METHODS

The study was conducted at KMC hospitals Attavar and Ambedkar circle, Mangalore. The data was collected for five months (March to July, 2013) and 173 cases were obtained. The records pertaining to the patients with FNA diagnoses of thyroid were checked. All the non-neoplastic and benign lesions were considered for the study. The TFT results and clinical findings were noted. Review of the slides was undertaken when thyroid function discrepancy was noted. SPSS version 13 was used for statistical analysis. This study was fully approved by our institutional review board. Thyroid FNA was performed without dermal anesthesia by aspirating blindly on the nodule or diffusely enlarged nodular/ smooth thyroid gland with a 23-24-gauge needle. At least two and at most, three aspirations were performed. The material obtained was dropped consecutively on rows of glass slides near the frosted end and immediately smeared by sliding another glass slide on it, akin to making a

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peripheral smear. The slides destined for Papanicolaou stain were immediately dropped in a Coplin jar with 100% methanol in it. The air-dried smears were stained with May-Grunwald-Giemsa. Since the Papanicolaou Society of Cytopathology Task Force on Standard of Practice does not specify the number or clusters or tissue fragments of thyroid follicular cells, we accepted a cluster consisting of at least 10 cells and five to six such clusters to be adequate.[2] The additional criteria used were 1) a clean background 2) cells not entangled in blood so that visibility is not interfered with.[3]Carnoy solution was used if the smears were very bloody.[1]

RESULTS

A total of 173 patients, who had their FNAs and thyroid function tests conducted at KMC, Ambedkar circle were included in the survey that included 3 cases of granulomatous thyroiditis(GT), 43(24.85%) cases of Hashimoto thyroiditis(HT), 126(72.83%) cases of multinodular goiter(MNG) and 1 case of unclassified thyroiditis.

The age range of the patients involved in the study was 20 years to above 60 years (Table 1). Of these, 149(86.1%) were females and 24(13.8%) were males. Fifty four patients belong to the age group of 41 to 50 years, the highest of all age groups (significant, Ï 2=16.855, p=0.0021). The mean age of the patients in this study was 42 ± 12.85(S.D) years. For the males, the mean age was 48 ± 14(S.D) years; for the females, the mean age was 41 ± 12.26(S.D) years.

Age	Frequency	Percent
20-30	39	22.5
31-40	41	23.7
41-50	54	31.2
51-60	24	13.9
Above 60	15	8.7
Total	173	100

Table 1: Shows the number of patients in each age groups

148(85.5%) of the lesions were cellular, 23(13.3%) were low to moderately and 2(1.2%) were minimally cellular. The general observations in MNG cases were of thyroid follicular cell sheets (Figs.1A, 1B) along with variable amounts of colloid. Most of the aspirates demonstrated thin colloid, only a handful revealed thick material (Fig.1C). Most of these cases displayed colloid or hemosiderin-laden macrophages, but a few, despite an extensive search failed to exhibit any. An impression of colloid goiter was conferred upon these cases. A small number of aspirates also illustrated large sheets with a microfollicular pattern(Fig.1D) but with scant colloid and few foamy cells in the background; a suggestion of hypercellular nodule in colloid goiter was provided in these.

The cases of HT(Fig.2C & D) were difficult to diagnose in a small subset of patients. Particularly, when the smears showed streaked lymphocytes with colloid in the background and follicular cells in the foreground, they were confounded with smearing artifacts (Fig.2A & B). Plasma cells, even if occasional could be appreciated in full-blown HT though they were absent in lymphocytic thyroiditis.

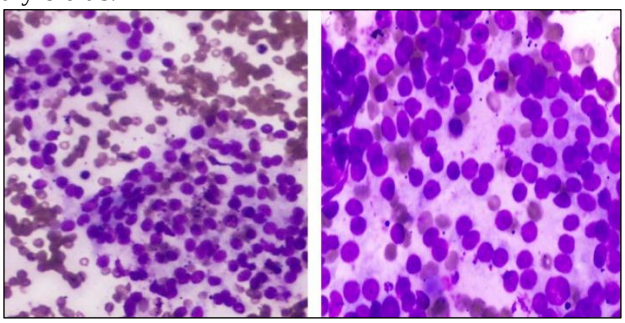

Fig 1A, 1B- Nodular colloid goiter with follicular cell sheets, MGG X100 (1A), MGG X 400 (1B)

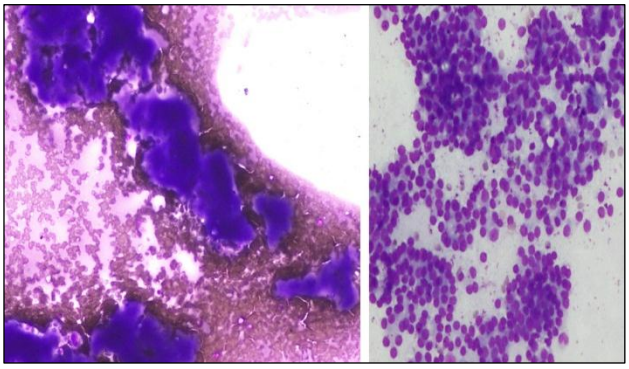

Fig. 1C: Abundant thick colloid, MGG X100 , Fig. 1D: Hyperplastic nodule in MNG, MGG X 100

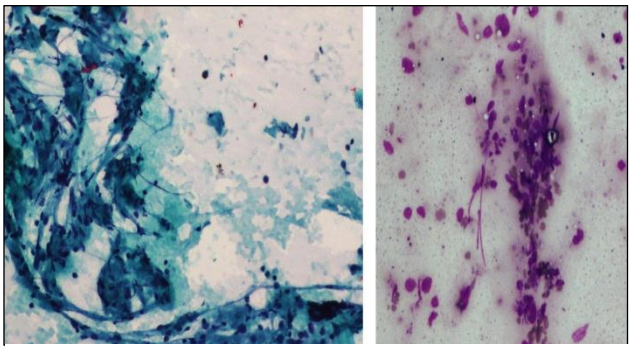

Fig. 2A: Follicular cells entangled in colloid infiltrated with lymphocytes in Hashimoto thyroiditis, PAP X100 Fig. 2B: Lymphocyte streaking in Hashimoto thyroiditis, PAP X 100

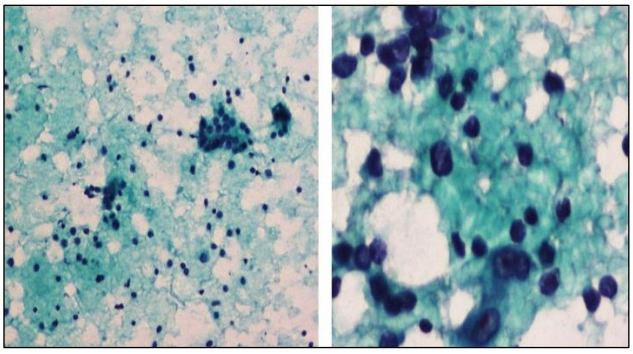

Fig. 2C: Follicular cells infiltrated and surrounded by lymphocytes and reactivated lymphoid cells in Hashimoto thyroiditis, PAP X100, Fig. 2D: Hurthle cell change in Hashimoto thyroiditis, PAP X 400

Amongst the patients surveyed, 18(10.4%) had high, 3(1.7%) had low and 152(87.9%) had normal T3 levels;

10(5.8%) had high, 18(10.4%) had low and 145(83.8%) had normal T4 levels. Hurthle cell changes were present among the aspirates of 69 patients with HT(n=32, 46.37%), MNG(n = 35, 50.72%) and GT(n = 2, 1.15%) cases. HT(n = 43) was significantly associated with Hurthle cell change (chi-square = 23.81, p < 0.0001). This has a margin of error 7.5%, confidence level 90%, and response distribution of 40%. 163 patients showed colloid (112 abundant, 4 moderate, 36 scant, 4 thick and 5, thick blobs of colloid in their aspirates) while 10 did not. Scant to absent colloid was found in 46 aspirates with 33 HT cases, 9 MNG, 2 GT and 1 unclassified thyroiditis and significantly associated with HT(Ï 2 = 25.68, p < 0.0001). Again, 37 of these 46 cases showed good cellularity in the aspirates (chi-square = 29.76, p < 0.0001). These two values had a margin of error 8%, confidence level 90% and rate of 70-80%.

Levels of TSH did not show any relationship to FNA diagnoses as a whole(Table 2). 84/126 of MNG cases had associated normal levels of TSH (p < 0.0001). Twenty two and 20 cases of 126 MNG cases were hypothyroid and hyperthyroid respectively and could not be significantly correlated(p = 0.15 and 0.20 respectively). No significant correlation between the various FNA diagnoses and the levels of T3(Fishers's exact test, p = 0.195) or T4(Table 3) could be established. Table 4 correlates FNA diagnoses with the type of colloid present in the aspirates. With reference to thick and thick blobs of colloid, FNA diagnoses had a highly significant correlation. T3(Fisher's exact test, p=0.823; Fisher's exact test, p=0.823) or T4(Fisher's exact test, p=0.592; Chi-square=0.244, p=0.885) levels did not correlate significantly with the various age groups and gender of the patients respectively. TSH levels too did not significantly correlate with age groups(chi-square=6.069, p=0.639) or gender(chi-square=4.377, p=0.122).

FNA Diagnosis	TSH levels –N(%)		
	Low	Normal	High
GT	0(0)	3(1.7)	0(0)
HT	6(3.4)	12(6.9)	25(14.4)
MNG	20(11.56)	84(48.5)	22(12.7)
Unclassified Thyroiditis	0(0)	1(0.5)	0(0)

Fishers exact test p=.900, NS

Table 2: Shows the correlation between FNA diagnoses and levels of TSH in each category.

FNA diagnosis	T4 levels-N(%)		
	Low	Normal	High
GT	1(0.57)	2(1.1)	0(0)
HT	3(1.7)	38(21.9)	2(1.1)
MNG	14(8.1)	104(60.1)	8(4.6)
Unclassified thyroiditis	0(0)	1(0.57)	0(0)

Fishers exact test p=.594, NS

Table 3: shows the relation between various FNA categories and T4

54.87%(95/173) of the total patients surveyed had abnormal TFT(Table 5). An abnormal TFT did not correspond to any benign pathology under study significantly. The patients diagnosed as HT(Table 6) were either hypothyroid (subclinical or clinical, n=25), hyperthyroid (n=6) or had a normal TFT (n=12). With respect to hypothyroidism, HT correlated significantly(chi-square = 14.535, p = 0.0007). The subclinically hypothyroid and euthyroid cases were 23(53.48%) and significantly correlated to HT(Ï 2 = 12.3, p = 0.0021). This had a margin of error 9%, confidence level 90% anda response rate of around 60%. The mean age of the HT cases was 38 ± 12.32 years.

FNA diagnosis	Type of colloid present				
	Absent	Abundant	Moderate	Scanty	Thick blobs
GT	0(0)	1(0.57)	0(0)	2(1.1)	0(0)
HT	5(2.8)	5(2.8)	3(1.7)	28(16.1)	2(1.15)
MNG	5(2.8)	106(61.2)	3(1.7)	5(2.8)	7(4)
Thyroiditis	0(0)	0(0)	0(0)	1(0.57)	0(0)

Fishers exact test p=.0001, HS

Table 4: shows various FNA diagnostic categories and type of colloid in aspirates

FNA diagnosis	Normal TFTs n(%)	Abnormal TFTs n(%)
GT	2(1.15)	1(0.57)
HT	12(6.9)	31(17.9)
MNG	63(36.4)	63(36.4)
Unclassified thyroiditis	1(0.57)	0(0)

Fishers exact test p=.717,NS

Table 5: shows various FNA diagnostic categories and type of colloid in aspirates

TFT normal	Subclinical hypothyroidism		Clinical hypothyroidism	Hyperthyroidism
	TSH<10 micro IU/ml T3 and T4 normal	TSH<10 micro IU/ml T3 and T4 low		
12	11	0	14	6

Table 6: shows the thyroid function status in HT patients

Perhaps due to the benign nature of the lesions, correlation was available in only 46 cases. Out of the 44 cases, four (4/46, 8.7%) were neoplastic. Three of them were papillary carcinomas in MNG. All of them were cystic, and the carcinomas occupied a focal area (approx. 0.5cm) in the wall of the cyst. Thus the false negative rate is (3/46, 6.5%) though this is not the actual false negative rate since histopathological diagnoses of all the cases were not available. The fourth one was a follicular adenoma, albeit a toxic one in a background of HT; the TFT had also revealed hyperthyroidism.

DISCUSSION

This study was done to emphasize thyroid function disorders in patients suffering from goiter. The malignant diseases were excluded because it was immaterial whether they suffered from TFT abnormalities. However, false negatives exist on FNA diagnoses ranging from 2 to 7%.[4] In a landmark study by Raab et al, a false positive diagnosis was made in 25% and false negative in 9.9% on the FNA of the thyroid.[5] The current study obtained histological diagnoses in only 46/173(26.6%) cases, and a false negative was seen in 3/46(6.5%), but this may not be significant because extremely low fraction of the study population was available for correlation.

As borne out by many studies in thyroid cytology in the past[6,7], the patient distribution in this study was heavily skewed towards the female gender. The age group of 41-50 years had more patients than the rest of the groups, and this was significant. In the present study, the mean age of the patients was 42 ± 12.85, comparable to that of Stai et al (47 ± 14)[7] but more than that of Kini et al(31.63)[6]. However, for the HT patients the mean age was 38 ± 12.32 years in the current study, approximately 6& ½ years greater than and 9 years less than that of the studies done by Kini and Stai et al respectively.[6,7]

MNG claimed a large majority of the patients distantly followed by that of HT in the current study, 72.83% and 24.85% respectively as opposed to 19.8% and 69.2%, correspondingly in the study done by Kini et al.[6] The cases showing features of both MNG and HT in the current study were categorized into either one depending upon the predominant pattern.

Most of the aspirates were cellular in the current study. The average rate of inadequate aspirate is 17%.[5] A recent report also puts the inadequacy at 10.4%.[8] Two (1.15%) aspirates in the study had very few cells, yet diagnoses were attempted and given as MNG. Their histopathological diagnoses were not solicited. High cellularity in the aspirates was significantly associated with scant colloid in the present study, the importance of which is still not appreciated.

Scant to absent colloid was seen in 46 cases. Thirty-three cases of HT were significantly associated with scant colloid($p < 0.0001$) though other studies have not mentioned such an association. Thirty-two of 43 patients with HT had Hurthle cells($p<0.0001$, highly significant). Out of 69 cases with Hurthle cells, the majority(35, 50.72%) are claimed by the MNG category. Association of Hurthle cells with HT is a well-known diagnostic criterion and is reported to be so by Kini and Stai et al.[6,7] In our study, lymphocytic thyroiditis and Hashimoto's thyroiditis were considered as one entity since the management of both is the same.[6]

T3 and T4 levels were disregarded to determine the prevalence of HT[7] and also in the medical management of minimally enlarged thyroid with HT, wherein TSH levels was deemed essential.[6] Likewise, we too have not found any significant correlation of either T3 or T4 with age groups, gender or FNA impression in the current study.

Though TSH levels did not correlate significantly in general with age groups, gender or FNA impression,HT correlated significantly with hypothyroidism($p = 0.0007$). Clinical and subclinical hypothyroidism is distinguished by elevated TSH levels above and below 10 microIU/ml respectively[6] based on NHANES III study normative data for TSH distribution.[9] Subclinical hypothyroidism is determined by TSH levels between 5 and 10 microIU/ml with normal T3 and T4 levels.[6,7] Of the 43 cases in our study, 14(32.6%) were clinically hypothyroid and 11(25.6%) suffered from subclinical hypothyroidism in contrast to 46(45.1%) and 9(8.8%) out of 102 patients respectively in the study by Stai et al.[7] In addition, the patients with normal TSH levels in our study(n=12,28%) is appreciably less than that in the study by Stai et al (n=47,46.1%).[7] However, the studies by Kini[6] or Stai et al[8] did not report any Hashitoxicosis, while our study had six(14%) patients withcytologic evidence of HT and thyrotoxicosis. The usual clinical course in these patients, who are mostly females between 3rd and 6th decade, is to ultimately culminate in clinical hypothyroidism.[10] The number ofeuthyroid and subclinically hypothyroid HT cases (23,53.48%) is significant ($p=0.0021$) in the current study. Though the effects of treating subclinical hypothyroidism are hitherto untested as prospective clinical trials are unavailable, yet potential benefits of treatment are worth mention. Evolution to absolute hypothyroidism and thereby its consequent morbidity may be halted; serum lipid profile, the normalization of which depends on adequate thyroid hormone levels may improve and thus chances of cardiovascular complications may be reduced and psychiatric and cognitive abnormalities resulting from mild hypothyroidism may be negated.[6] The euthyroid and subclinically hypothyroid patients are the main beneficiaries of anticipatory thyroid hormone replacement therapy. Clinically, these euthyroid patients should be observed for signs of progression to overt hypothyroidism. The sporadic incidence of such cases developing antithyroid antibodies particularly in child-bearing women in pregnancies is noteworthy.[6] Since hypothyroidism in the mother produces miscarriage, fetal and neonatal death[7] and low intellect in the progeny, cytologically proven euthyroid or subclinical hypothyroid HT cases need observation and follow-up and if pregnant, need supplemental thyroxine to prevent potential mishaps associated with hypothyroidism.

Screening for HT may also be done by anti-TPO antibodies along with TFT. However, 18.7% overt hypothyroid cases and 50% euthyroid andsubclinically hypothyroid cases reported negative for this antibody in the study done by Stai et al.[7] Moreover, in a study by Rago et al, moderate to severe lymphocytic infiltration was found in thyroid gland histology of 52.4%(64/122) of patients having elevated levels of thyroid antibodies (TPOAb or thyroglobulin antibody, TgAb) and 11.8%(53/448) of the patients with negative thyroid

antibodies and this correlation was statistically significant.[11] Conversely, a large number of patients also failed to show substantial lymphocytic infiltration in follicular epithelium even with raised level of thyroid antibodies.[11] Thus, testing for antithyroid antibodies should be viewed as an ancillary test procedure rather than an essential one. It was also hypothesized that cytological evidence of HT heralds positive clinical diagnosis.[7]

Some authors believe that thyroid nodules with high TSH levels portend increased risk of differentiated thyroid cancer.[12]Rago et al in their study of 570 indeterminate nodules on cytology concluded that clinical and pathological measures of thyroid autoimmunity concurred with each other but association with malignancy lacked sufficient proof.[11] The incidence of thyroid carcinomas could not be linked to circulating TgAb, TPOAb or extranodular lymphocytic infiltration on histology.[11] Therefore, we support the hypothesis that the risk of thyroid malignancy in HT is unfounded; irrefutable evidence of such an association is still wanted though arguments in favor of carcinogenesis due to continued inflammation[7] is tempting and may seem credible to some authors.

Thick blobs of colloid significantly associated with MNG or HT in the current study. Comparable studies have not been found on this aspect. It however, be claimed with little reservation that thick blobs of colloid on smears should indicate a diagnosis of MNG or HT, rather than any other forms of thyroiditis.

Just as studies done by Stai et al and Kini et al revealed unexpectedly high numbers of HT patients on cytology[6,7], it is surprising that a large majority of the patients in the current study suffered from MNG. Stai et al had drawn a parallel prevalence between HT and diabetes mellitus type II(DM2).[7] An overwhelming number of MNG cases from an iodine sufficient area in the current study prompted us to compare its prevalence to that of DM2. This observation is perplexing as traditional reason dictates iodine deficiency to instigate the MNG process. A familial, metabolic or HLA association may not be unlikely.

Small papillary carcinomas in cysts may be aspirated by ultrasound guidance to curtail false negatives.[13] Even if technical aspects like inadequate cellularity daunt positive expectation of minimizing false negatives, lack of standardization of diagnostic categories, which is a pathologists' problem, obviates arriving at precise impression.[5] Cytologists use diverse norms for various diagnostic classes like atypical and follicular lesion or neoplasm.[5] Unanimous guidelines to reach a transparent set of diagnoses are eagerly awaited that are concordant with both the clinician's deduction and pathologist's reasoning.

CONCLUSION

The majority of the benign goiter cases in the present study consisted of MNG cases. HT was significantly associated with hypothyroidism. The major observation in this study is the subset of euthyroid and subclinically hypothyroid cases(23/43, 53.48%) of HT($p = 0.0021$), who should be the main beneficiaries of anticipatory thyroid hormone replacement therapy leading to obviation of the deleterious effects of frank hypothyroidism. Antithyroid antibodies are an unreliable measure of this condition, and so FNA is the sole diagnostic modality in these patients.

HT was also significantly associated with scant colloid($p < 0.0001$) and Hurthle cell change($p < 0.0001$). Thick blobs of colloid were significantly associated with MNG and HT. In addition, high cellularity of the aspirates correlated significantly with scant to absent colloid($p < 0.0001$) though the diagnostic implication of such an observation is yet to be pondered into. In contrast to the existing studies, the current study had a very low rate of inadequate cellularity(1.15%), but a diagnosis was attempted in both. False negatives 3/46(6.5%), though available on a meager and selected subset of the patient population is still within the range of published data.

Though changes relating to both multinodular goiter and Hashimoto thyroiditis are found in thyroid parenchyma adjacent to thyroid epithelial malignancies, it has not yet been categorically proven that Hashimoto thyroiditis is associated with or gives rise to such carcinomas.

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