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Comparative study on semi-quantitative grading of lymphocytic thyroiditis with biochemical parameters - with an insight into its cytomorphological aspects

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Abstract
Lymphocytic thyroiditis (LT) embraces a heterogenous group of thyroiditis and Fine Needle Aspiration Cytology (FNAC) provides a safe and reliable method of diagnosing it. This present study was undertaken to analyze and grade Lymphocytic thyroiditis on cytology smears and compare the severity of thyroiditis with Thyroid Function Tests (TFT). Periodic assessment of Thyroid Function Tests and sub-classification of Lymphocytic thyroiditis on FNAC assists in early diagnosis of Lymphocytic thyroiditis and helps to monitor the progression of the disease state.

Materials and methods: This prospective study was conducted on 150 patients attending FNAC clinic at a tertiary level care hospital over a period of two years. Various parameters like Clinical signs & symptoms, Thyroid Function Tests, FNAC of thyroid gland, semi- quantitative grading on cytology smears were noted and results were analysed statistically.

Results: One hundred and fifty patients diagnosed as Lymphocytic thyroiditis on FNAC, showed a female predominance (96.7%) with a peak age group between 21-30 years. Clinically majority of them had a diffuse thyromegaly (88.0%) and 48.0% were biochemically hypothyroid. On sub-classifying cytology smears, Grade 1(mild) Thyroiditis was noted in 20%, Grade 2(moderate) in 64.0% and Grade 3(severe) in 16.0% of the cases. Few cases showed the presence of abundant colloid associated with LT in 22.0% of the cases. Positive Statistical association was seen between Grade 3 Lymphocytic thyroiditis and TSH levels (p=0.03), while Grade 1 & 2 of Lymphocytic thyroiditis did not show any correlation.

Conclusion: Despite the availability of several tests in diagnosing Lymphocytic thyroiditis, FNAC remains a gold standard test, especially in early stages of the disease. Co-existence of Lymphocytic thyroiditis & colloid is not unusual, particularly in post-iodization era.

Keywords: Cytologic grading, FNAC, lymphocytic thyroiditis, thyroid function tests

Introduction

Thyroid diseases are becoming common, disruptive, expensive but treatable. Many of the thyroid diseases are also preventable. Numerous studies support these descriptions: (1) Common-anywhere from 5-20% of the world wide population have some thyroid abnormality, depending on the indicator chosen. This fraction increases in certain subpopulations (e.g. autoimmune disease in older women), (2) Disruptive – both hypothyroidism and hyperthyroidism impair physical and mental performance, produce morbidity, and pose special risks for pregnancy and the developing fetus (3) Expensive – Testing of thyroid function is a routine laboratory procedure costing millions of rupees annually. (4) Treatable – Highly satisfactory therapies exists for all the common problems: hyperthyroidism, hypothyroidism, nodules, cancer, and iodine deficiency, and (5) Preventable – the consequences of iodine deficiency are readily avoided by optimal iodine nutrition, appropriate diagnosis and treatment can keep at bay the effects of hypothyroidism on human development. Avoidance of excess iodine can prevent many of its complications, including goiter, hypothyroidism, hyperthyroidism and autoimmune disease [1].

The term Hashimoto's thyroiditis (HT) and Lymphocytic thyroiditis are used synonymously by many authors while diagnosing autoimmune thyroid diseases on cytology [2, 3, 4, 5]. It is a classic form of destructive auto-immune thyroiditis and its diagnosis is based on clinical, cytomorphological and serological parameters [2, 6, 7]. The cytomorphologic markers include lymphocytic infiltration of the interfollicular space, invasion of follicles by the lymphocytes and later, total destruction of follicles.

In the long run, the follicular architecture is totally destroyed and replaced by fibrosis. The early active phase of disease is transient with clinical manifestations of thyrotoxicosis while the evolution phase and destructive phase manifest with subclinical or overt hypothyroidism.[4,5]
Grading of thyroiditis has been carried out on histological specimens in the past based upon number of foci of lymphocytes per standard representative section. On the other hand grading on cytology smears has been done by only a few workers [8, 9, 10].
By applying the simple, practical & easily applicable criteria devised by Bhatia *et al*. [11] 150 cases of Lymphocytic thyroiditis in the present study were categorized into Grade 1-mild, Grade 2 –moderate & Grade 3- severe thyroiditis.
Various studies have highlighted the importance of TSH in assessing the clinical severity of the disease and also its importance in monitoring the patients who are on treatment with anti thyroid drugs [6, 12, 13, 14, 15, 16]. The importance of combined, clinical, biochemical, serological and cytomorphologic approach has also been emphasized [17]. Nonetheless, the utility of FNAC in diagnosis of serologically negative & early cases remains non replaceable.
In the present study attempt has been made to compare the severity of thyroiditis on cytological smears with that of Thyroid Function Tests. Also the presence of less common cytomorphologic features like background colloid, fire-flares and lymphoid tangles has been highlighted.

Materials and methods

This prospective study was carried out over a period of two years. A total 150 cytological proven cases of Lymphocytic thyroiditis were included in the present study while other specific/infectious thyroiditis and those which are associated with neoplasms were excluded. After obtaining informed consent, relevant clinical details like presence or absence of thyroid dysfunction, nature of thyroid enlargement (diffuse/nodular/solitary nodule) were noted. All patients were subjected to Thyroid function tests.
Individuals with visible and or palpable thyroid were subjected to FNA of thyroid gland. Aspirations were performed by a standard procedure using 23-24 gauge needle attached to a 5 to 10 ml syringe. Better visualization of thyroid was accomplished by placing the patient in a supine position with the small pillow beneath the shoulder and upper back so that the neck is fully extended. An average of 2-4 thin, evenly spread smears were prepared and air dried for Romanowsky staining as well as wet fixed in 95% ethanol, for staining with May-Grunwald-Giemsa, H&E and Papanicolaou method respectively.
A detailed examination was done on cytology smears, which were categorised according to cytological yield as low or highly cellular. Following Features were noted: Amount and nature of back ground colloid, Hurthle cell change, Spectrum of reactive lymphoid cells, including plasma cells, lymphoid globules, anisonucleosis of thyroid follicular cells, other cellular components like macrophages, epitheloid cells, multinucleated giant cells, eosinophils and presence or absence of the fire flares.
For the serological correlation, severity of thyroiditis was graded as per the criteria devised by Bhatia *et al*. [11].

Table 1: Grading of Thyroiditis

Grade	Morphological features
Grade I (Mild)	Few lymphoid cells infiltrating the follicles /increased number of lymphocytes in the background.
Grade II (Moderate)	Moderate lymphocytic Infiltration or mild lymphocytic infiltration with Hurthle cell change/giant cells /anisonucleosis.
Grade III (Severe)	Florid lymphocytic inflammation with germinal center formation, very few follicular cells left.

The total tri-iodothyronine (T_3) and thyroxine (T_4) levels were measured by the radio immune assay method using Immuno tech (Beckman Coulter Company, Crech Republic) kits. Thyroid stimulating harmone (TSH) levels were determined by immunoradiometric assay system,using Turbo TSH (^{125} I) IRMA kit

Table 2: Normal range of TFT

TFT	Normal Range
T3	70-200ng/dl
T4	5.52-13.5ug/dl
TSH	0.17-4.0uIU/ml

Statistical analysis was done using Chi-square test, ANOVA test, independent sample T-test & pearson's correlation (p value). A p-value of ≤ 0.05 was considered statistically significant.

Results

Out of 150 patients, female predominance (97%) was observed with peak age group was between 21-30 years. Clinically most of the patients presented with diffuse thyromegaly (88%)
Serologically majority of the patients were biochemically hypothyroid (48.0%), while subclinical hypothyroidism was noted in 40.7% of the cases.

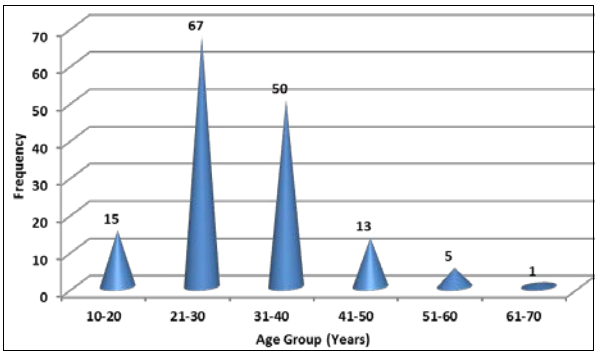

Table 3: Serological findings based on TFTS's

Based On Tft	No. of Cases	Percent (%)
Hypothyroid	72	48.0
Subclinical Hypothyroid	61	40.7
Euthyroid	11	7.33
Hyperthyroid	06	04
Total	150	100.0

Cytomorphological features- 118 of the cases (78.6%) represented high cellular yield while Lymphocytic thyroiditis with follicular hyperplasia was seen in 6 (4.0%) cases and abundant colloid was seen in 33 (22.0%) cases. 139 cases showed predominance of lymphocytic infiltration, Hurthle cell change was seen in 62 cases, multinucleated giant cells in 59 cases, 53 of the cases showed anisonucleosis in 53 cases while epitheloid cells and plasma cells were seen in 36 and 29 cases respectively.

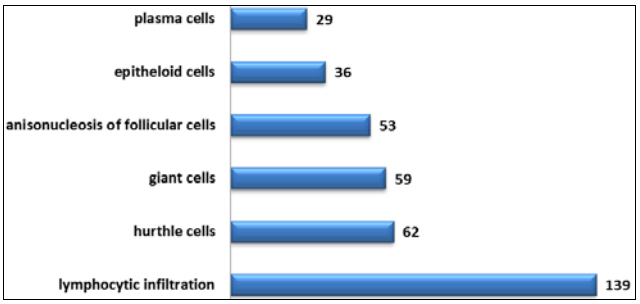

Fig 2: Cytomorphological findings in lymphocytic thyroiditis

Semi-quantitative grading of lymphocytic thyroiditis on cytology smears revealed, 30 cases (20.0%) represented Grade 1 (mild) thyroiditis, 96 cases (64%) in Grade 2 (moderate) thyroiditis and 24 cases(16.0%) in Grade 3(severe) thyroiditis.

Table 4: Cytological Grading of chronic thyroiditis

Grade	No. of Cases	Percent
I (Mild)	30	20.0
II (Moderate)	96	64.0
III (Severe)	24	16.0

Comparative study between Thyroid Function Tests and Cytological gradings revealed a statistically significant association with TSH and Grade 3 thyroiditis (p=0.03), while no association was found with T3 and T4.

Table 5: Correlation between TFT & Cytological grading Using ANOVA-TEST; statistically significant association was observed between TSH levels and Grade 3 thyroiditis (P= 0.03).

TFT	I n=30	II n=96	III n=24	Significance (p -Value)
T3	0.8 ± 0.45	1.22±2.0	0.76±0.58	0.33
T4	5.17±2.37	5.3±5.5	5.1±5.2	0.98
TSH	15.62±18.22	26.50±27.53	35.06±33.06	0.03

Discussion

The term "Lymphocytic thyroiditis" embraces a heterogeneous group of thyroiditis and represents different phases of organ specific immune mediated inflammatory disease and characterised by the production of auto-antibodies which functionally alters the Thyroid Functions [2, 3, 18, 19].

FNAC of thyroid provides a safe and accurate method for diagnosing Lymphocytic thyroiditis [11]. Cytomorphological features are dependent on the phase of disease progression. Early in the disease abundant lymphocytes are present and later Hurtle cell change predominate while fibrosis is seen towards end of destruction phase [20, 21].

In the present study 150 cases of Lymphocytic thyroiditis were studied and compared with Thyroid Function Tests (T3, T4 & TSH). The severity of throiditis was graded on cytology smears using criteria defined by Bhatia *et al.* [11]

Most of the patients in the present study were females, with female: male ratio of 32:1,which is similar to the study conducted by Kumar *et al.* [9], while Jayaram *et al.* [22] documented 10:1.The age ranged between 12 & 64 years with a mean age of 38.02 was noted. Significantly, most of the cases were documented in a population somewhat younger age group, that is described in the literature [23, 11].

Clinically, most of the patients in the present study presented with diffuse thyroid enlargement (88.0%), mulinodular enlargement & solitary nodule were encountered in 8.7% and 3.3% of the cases respectively. Similar observations was made by Singh *et al.* [4] while study conducted by Friedman *et al.* [23] showed 80.0% of nodular presentation. The nodules represent early stage of the disease, even before the clinical signs become evident.

On biochemical evaluation (Thyroid Function Tests) most of the patients were hypothyroid (48.0%), sub-clinical hypothyroidism was noted in 40.0% of the cases, euthyroid in 7.5% and hyperthyroid state in 4.0% of the cases, which was similar to the observations made Singh *et al.* [4], where 58% of patients were found hypothyroid, 19 % of them were having subclinical hypothyroidism, 23.0% were in euthyroid state. On the otherhand a study conducted by Bhatia *et al.* [11], found 98.68% of patients had subclinical hypothyroidism.

FNAC of the thyroid gland is a preferred choice of diagnosing Lymphocytic thyroiditis, especially in sub-clinical and biochemical euthyroid state [9]. Multiple aspirations are helpful for diagnostic accuracy and its usefulness has been stressed by Hamberguer *et al.* [24] In the present study high cellularity was noted in 78.6% of the cases also the FNA yield depends on several other factors like technique of aspiration, type of thyromegaly, presence of colloid and follicular hyperplasia [23].

The hallmark of Lymphocytic thyroiditis is the inflammatory component i.e., infiltration of reactive lymphoid series of cells inclusive of plasma cells into the follicular epithelial cell clusters. The presence of lymphoid tangles are also described by many authors [9, 11, 25]. Plasma cells can be of great help especially in diagnosing early stages of Lymphocytic thyroiditis, seen mainly towards the periphery of the smears as described by Jayaram *et al.* [26] and also documented infiltration of eosinophils in 17% of their cases.

In the present study reactive lymphoid cells were observed in 86.0% of the cases. Grade 3 thyroiditis showed florid infiltration of reactive lymphoid cell population, few with germinal centre formation and tangible body macrophages. Occurrence of multinucleated giant cells has been frequently described in CLT/HT. Various studies have reported them in 28 – 58% of the cases [9, 22, 27]. In the present study it was seen in 39.3% of cases. Plasma cells were seen in 19.4% of the cases where as no eosinophilic infiltrate was observed.

Classically absence of/scanty colloid is feature of Lymphocytic thyroiditis, as it is associated with destruction of follicles and depletion of colloid in severe degree of throiditis [2, 3, 6, 7]. However, various authors have emphasized the presence of colloid in early stages of Lymphocytic thyroiditis [3, 4, 6, 9, 11]. In the present study, colloid material was seen in 22.0% of the cases, whereas Kumar *et al.* [9], documented colloid in 36.0% of the cases. A

careful search revealed its presence is associated with Grade 1 (mild) thyroditis.

The literature reveals that thyroid autoimmunity is uncommon in iodine deficient areas, but becomes prevalent with an improvement in iodine supplementation [28]. Universal salt iodization could have led a rise in the incidence of auto-immune disease in patients with a pre-existing colloid goiter.

Semi-quantitative grading of Lymphocytic thyroiditis was initially done by Kumar *et al*. [9] using two tier grading system as: 1) Minimal (61.9% cases) and 2) Moderate to heavy lymphocytic infiltration (38.1% cases) and found a statistically significant correlation with hormonal status of the patients (p= 0.02).

In the present study Lymphocytic thyroiditis was sub-classified as Grade 1 (mild), Grade 2 (moderate) and Grade 3 (severe) in 20.0%, 64.0% and 16.0% of the cases respectively as per criteria devised by Bhatia *et al*. [11] It was found that Grade 1represented the classical form of Chronic Lymphocytic Thyroiditis while Grade 2 showed typical features of Hahimoto's thyroiditis like Hurthle cell change, epitheloid cell granulomas and plasma cells. Grade 3 throiditis represented florid type of Lmphocytic thyroiditis with reactive germinal centre formation and lymphoid tangles.

Bhatia *et al*. [11] defined and correlated the grade of thyroiditis with clinical, biochemical and ultrasonographic parameters, where as none of these parameters correlated in their study. In the present study though there was no association was observed between cytological gradings and TFT's (T3 & T4), a strong positive association was seen with TSH levels and Grade 3 thyroiditis (p=0.03), which emphasizes the fact that cytomorphological features appear much earlier than biochemical parameters becomes evident. This discrepancy among different studies may be contributed by other factors like dilution of blood, number of aspirations, cytological yield and competence of technical staffs. However, in serologically negative cases, and biochemically sub-clinical hypothyroidism, Fine Needle Aspiration proves to be a more affordable and reliable indicator of Lymphocytic Thyroiditis.

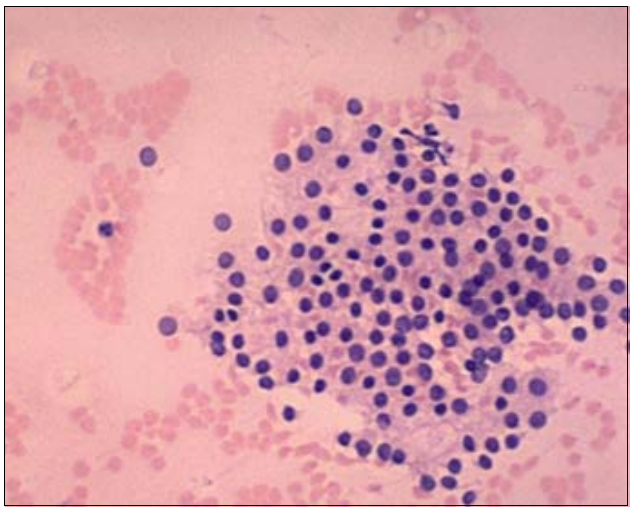

Fig 3: Mild lymphocytic infiltration seen among follicular cell clusters (H&E –100 X)

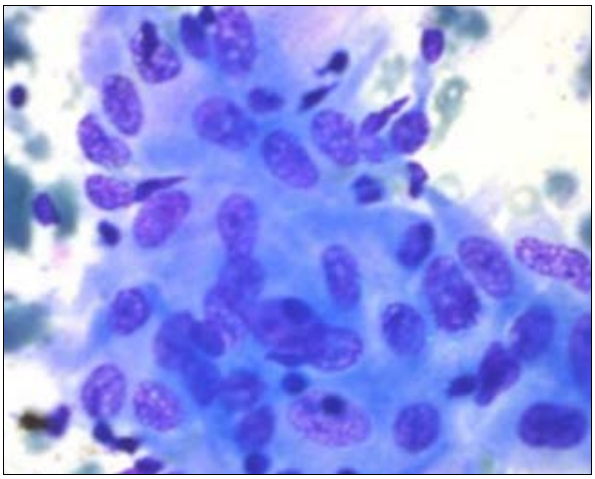

Fig 4: Grade II Thyroiditis Showing epithelioid cell granuloma, Hurthle cell change. (May-Grunwald-Giemsa, 400 X)

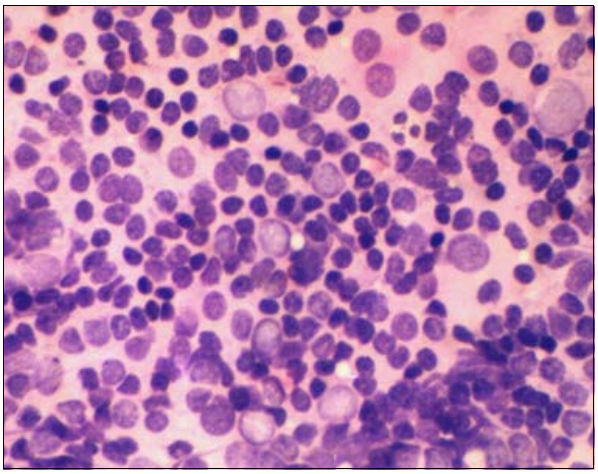

Fig 5: Florid lymhocytic thyroiditis, almost obscuring the follicular cells (H&E, 400 X)

Conclusion

This present study highlights the significance of FNAC, as a simple and more accurate method for diagnosing Lymphocytic thyroiditis which may be often missed on mere biochemical evaluation. Study of cytomorphologic features along with periodic evaluation of Thyroid function tests has to be considered in monitoring the progression of the disease. Presence of colloid in association with Lymphocytic thyroiditis should not exclude the diagnosis, particularly in post-iodization era.

References

1. Dunn JT. Guarding our Nation's Thyroid Health. J Clin Endocrinol Metab 2002;87(2):486-88.
2. Anirban Maitra. The endocrine system. In: Robbin and Cotran Pathologic basis of diseases. 8th edi: Saunder 2010,1107-118.
3. Rosai J. Thyroid gland. In: Rosai and Akerman's Surgical Pathology. 10th edi: Rosai J; New Delhi, Elsevier 2011,515-65.
4. Neha Singh, Surendra Kumar, Vir Singh Negi, Neelaiaah Siddaraju. Cytomorphological Stud of Hashimoto's thyroiditis and its Serologic Correlation. J Acta Cytologica 2009;53(5):507-516.

5. Orell SR, Philips J. Fine needle biopsy and cytological diagnosis of thyroid lesions. In:Orel text book cytopathology. 5th edi: Orell SR, Basel; Karger 2012,66-72.
6. Sanchez MA, Stahl RE. The thyroid, parathyroid and neck mases other than lymph nodes. In: Koss's Diagnostic Cytology and Its Histopathological Basis. 2nd edi: LG Koss, MR Melamed; New York, Lippincott Williams and Wilkins 2006,1155-1157.
7. Buley ID. The thyroid gland. In Diaggnostic Cytopathology. 2nd edi: W Gray, GT Mckee; Oxford, Churchill Livingstone 2002,577-601.
8. Waterhouse JP, Doniach I. Post-Mortem prevalence of focal lymphocytic adenitis of submandibular gland. J Path Bact 1966;91:53-64.
9. Kumar N, Ray C, Jain S. Aspiration cytology of Hashimoto's thyroiditis in an endemic area.Cytopathol 2002;13:31-9.
10. Volpe R. The pathology of thyroiditis. Hum Pathol 1978;19:429-38.
11. Bhatia A, Rajwanshi A, Dash RJ, Mittal BR, Saxena AK. Lymphocytic thyroiditis: Is cytological grading significant? A Correlation of grades with clinical, biochemical, ultrasonographic and radionuclide parameters. CytoJ 2007;4:10.
12. Jameson JL, Weetman AP. Disorders of thyroid gland. In: Harrison's Principle of Internal Medicine. 18th edi, Vol.2: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Lango DL, Jameson JL; New York, McGraw Hill Companies 2005,2104-2127.
13. Singh J, Marwaha V, Singh J, Sankar R, Dhillon HS, Nath BA. Clinical study of hypothyroidism. JAPI 1999;47(1):130-131.
14. Carcagiu ML. Thyroid gland-Danjanov I and Lidner J. Anderson's Pathology, 10th edi, St. Louis Missouri, Mosby Year Book Inc 1996;2:1943-1978.
15. Bhattacharjee S. A study on the presenting features of hypothyroidism and subclinical hypothyroidism. JAPI 1999;47:130.
16. Canaries GJ, Monowitz NR, Mayor G, Ridgway C. The Colrado thyroid disease prevalence study. Arch Intern Med 2000;160:526-34.
17. Juergen Kratzsch, Georg Martin Fiedler, Alexander Leihiltle. Thyrotropin and thyroid hormones based on National Academy of clinical biochemistry criteria and regular ultrasonography of the thyroid. J Clinical Chemistry 2005;51(8):1480-86.
18. Marshall SF, Meissner WA. Struma lymphomatosa (Hashimoto's Disease). Ann Surg 1955;141:737-746.
19. Roitt IM, Doniach D, Campbell PN. Autoantibodies in Hashimoto's disease (lymphadenoid goiter). Lancet 2,840.
20. MacDonald L, Yazdi YM. Fine needle aspiration biopsy of Hashimoto's thyroiditis. Sources of diagnostic error. Acta Cytol 1999;43:38-42.
21. Ian D Buley. Thyroid gland, Endocrine system. In: Diagnostic Cytopathology. 3rd edi: Winifred Gray, Gabrijela Kocjan; Elsevier 2001,487-509.
22. Jayaram G, Iyengar KR, Sthaneshwar P, Hayati JN. Hashimoto's thyroiditis; A Malasian perspective. J Cytol 2007;24:119-124.
23. Friedman M, Shimaoka K, Rao U, Tsukada K, Gavigan M, Tamura K. Diagnosis of lymphocytic thyroiditis (nodular presentation) by needle aspiration. Acta Cytol 1981;25:513-22.
24. Hamberger JI, Hamberger SW. Fine needle aspiration biopsy of thyroid nodules: avoiding the pitfalls. NY State J Med 1986;86:241-49.
25. Bagchi N, Brown TR, Parish RF. Thyroid dysfunction in adult over age of 55 years: A study in urban US Community. Arch Intern Med 1990;150:785-7.
26. Jayaram G. Thyroiditis. In: Atlas and Text of Thyroid Cytology. 1st edi: Jayaram G; New Delhi, Arya Publications 2006,24-30.
27. Guarda LA, Baskin HJ. Inflammotory and lymphoid lesions of the thyroid gland. Am J Clin Pathol 1997;87:4-22.
28. Okosieme OE, Taylor N, Gupta N, Verma K. Prevalence of thyroid autoantibodies in Nigerian patients. QJ Med 2007;100:107-112.