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Original Article

Pathology Section

Study of Correlation of Cytomorphological Features of Lymphocytic Thyroiditis with Biochemical Parameters and Vitamin D Deficiency

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ABSTRACT

Introduction: Fine Needle Aspiration Cytology (FNAC) of the thyroid is a reliable and common method used for diagnosis of chronic Lymphocytic Thyroiditis (LT) which is an autoimmune disease. Vitamin D (Vit D) deficiency, a prevalent health problem, is known to have correlation with various autoimmune diseases especially chronic LT.

Aim: To evaluate the relationship between Vit D levels, biochemical parameters with cytomorphological features of LT.

Materials and Methods: The present cohort study was conducted on 88 patients with cytological evidence of LT at a thyroid research centre in northern India between June 2017 to September 2018. Thyroid Stimulating Hormone (TSH), Antithyroid Peroxidase (ATPO) Antibody and Vit D levels along with patient's clinical presentation, and thyroid ultrasound were evaluated for all subjects. The cytological grades and other cytomorphological features were correlated with these parameters.

Results: Most of the patients were females (82, 93.2%) who presented with diffuse thyromegaly (69, 78.4%) and had hypothyroidism (58, 65.9%). By cytology grade I thyroiditis (40, 45.5%) was commonest followed by grade II (38, 43.2%). The Vit D deficiency and elevated ATPO were seen in 72 (81.8%) and 78 (88.6%) patients, respectively. Lowest level of Vit D (7.8±4.9 ng/mL) was seen in grade III patients. Significant correlation was observed between ATPO and Vit D levels with cytomorphological grades and some cytomorphological features like Hurthle cell change and plasma cells presence. While TSH levels correlated significantly with cytological grades only in hypothyroid group.

Conclusion: This study found that Vit D deficiency and ATPO levels significantly correlates with cytological grades of thyroiditis and affect certain cytomorphological features like plasma cells presence, suggesting lower levels of Vit D and higher ATPO may be related to more active disease.

Keywords: Antithyroid peroxidase antibody, Cytological grades, Hurthle cell

INTRODUCTION

The essential role of Vit D is to regulate bone and mineral homeostasis, besides that it has certain non skeleton actions like immune response, cancer signaling etc. Recently, studies have demonstrated that Vit D plays an important role in immunomodulation and its deficiency has been associated with many autoimmune diseases like systemic sclerosis, rheumatoid arthritis, type 1 diabetes, Systemic Lupus Erythematous (SLE) and autoimmune thyroiditis [1-3].

Chronic LT or autoimmune thyroiditis a synonym of Hashimoto's thyroiditis was first described by Hakuru Hashimoto in 1912. Autoimmune thyroiditis, the commonest cause of hypothyroidism, is characterised by an increased number of mature and transformed lymphocytes impinging on follicular cells leading to destruction of gland and progressive thyroid function failure [3,4]. Other features like Hurthle cell change, presence of plasma cells, histiocytes, epithelioid cell granuloma and anisonucleosis are also noted on cytology. Both cellular and humoral immunity play a role in pathogenesis of this autoimmune disease. The process starts with the sensitisation of T helper-cells to thyroid antigens and their activation leading to cytokines mediated cell death, recruitment of auto reactive B cells and antibody dependent cell-mediated cytotoxicity resulting in thyrocyte destruction.

The FNAC is a reliable and commonly used method of diagnosing LT. Bhatia A et al., were the first to distinguish cytomorphological grade LT from grade I (mild) to grade III (severe) based on the extent of infiltration of follicular cells by lymphocytes [4]. There after many studies have compared the cytological grades with hormonal and serological parameters [4-7]. Over past decade many studies have demonstrated higher prevalence of Vit D deficiency among patients of autoimmune thyroiditis [2,8]. However, correlation of Vit D deficiency and cytomorphological features of autoimmune thyroiditis has never been done. This study was done to correlate the cytomorphological features and grades with Vit D levels and other biochemical parameters.

MATERIALS AND METHODS

The present cohort study was carried out at a Thyroid Research Centre of northern India and was approved by the Ethical Committee of the Institution (IEC/ACMS/NP-1/2017). Total 796 patients had undergone FNAC of thyroid at our centre during June 2017 to September 2018. Out of which 88 fresh cases of LT were enrolled in this study after obtaining a written consent.

Inclusion criteria: Only recently diagnosed cases with cytological evidence of LT and no history of any other autoimmune disease were included in the study.

Exclusion criteria: Old cases already on medication or taking supplements and patients with Ischemic Heart Disease (IHD), neurological diseases, Chronic Renal Failure (CRF) or pregnancy were excluded from this study, as these could interfere with TSH and Vit D levels.

The FNAC of the thyroid was performed from multiple sites using 24G needle and both aspiration and non aspirational techniques. The smears were stained with Papanicolaou and Giemsa stain. Serum sample was collected for TSH, ATPO and 25(OH)D from all the patients. These parameters were estimated by an ElectroChemiLuminescence (ECL) immunoassay on Cobas e411, Roche, Germany.

The diagnosis of chronic LT was based on criteria- presence of increased lymphocytes in the background; lymphocytes/plasma cells infiltrating follicular cells; fine chromatin of follicular cells; and presence of Hurthle cells, anisonuclosis, epithelioid cells, giant cells and scattered fibroblast in aspirate [9,10]. Predefined cytological criteria as per Bhatia A et al., which was based on extent of lymphocytic infiltration ranging from minimal to florid and other features like Hurthle cell change, giant cells etc., were used for grading of the thyroiditis in present study [4].

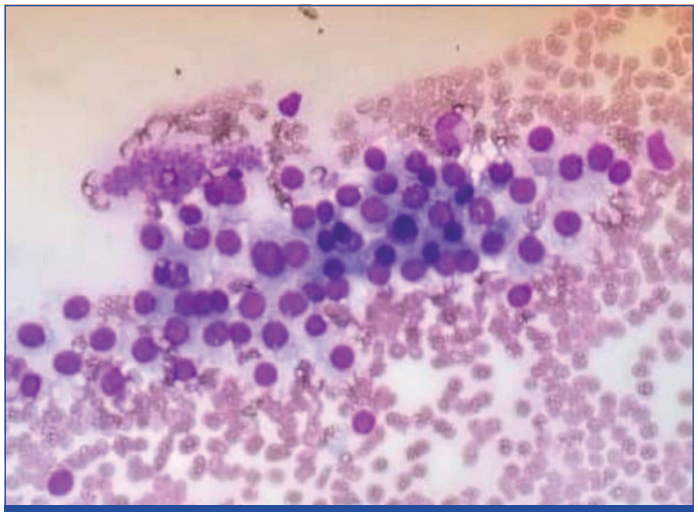
STATISTICAL ANALYSIS

Results were statistically analysed by Statistical Package for the Social Sciences (SPSS) 23.0 for Windows. The mean and the Standard Deviation (SD) for all the variables were calculated. Analysis of Variance (ANOVA) F test was used to compare the results of all cytological grades of thyroiditis in all studied groups. The thyroid functional state, ATPO state, and 25(OH)D state were correlated using chi-square (χ^2) tests, and p-value of <0.05 was considered significant. The correlation among serum Vit D levels, ATPO levels and TSH levels was done using Pearson correlation and presented by the correlation coefficient (r). Results were considered non significant or significant when p-value > or < 0.05, respectively

RESULTS

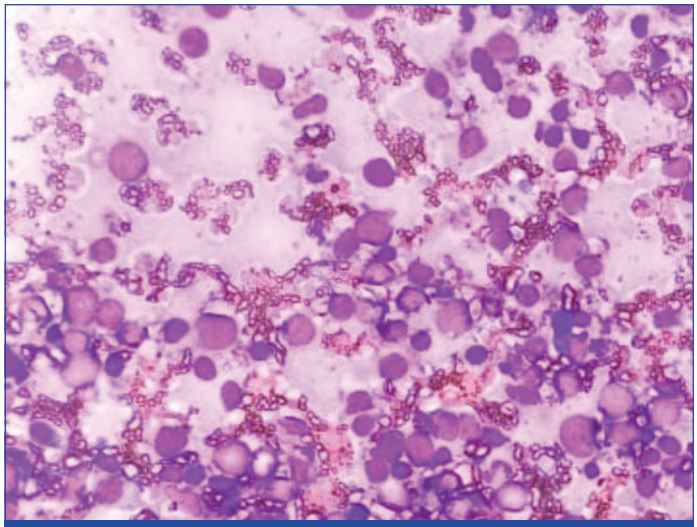
Total 88 patients who met the inclusion criteria were taken up for the study. Majority of patients (82/88, 93.2%) were females and only 6/88 (6.8%) were males. Diffuse thyroid swelling was most common presentation (69, 78.4%) while multinodular enlargement, solitary nodule and no goiter was noted in 13 (14.8%), 3 (3.4%) and 3 (3.4%) patients, respectively. On Ultrasound (USG) diffuse hypoechoic and heterogeneous echotecture was noted in 72 (81.8%) patients and hyperechoic macronodules >5 mm in 3 (3.4%). Normal study on USG was reported in 13 (14.8%) patients.

Smears of 40/88 (45.5%) patients a showed only mild lymphocytic infiltration so were graded as mild (grade I) [Table/Fig-1]. Moderate (grade II) thyroiditis was observed in 38 (43.2%) patients who showed Hurthle cell change, giant cells, anisonucleosis etc., along with mild to moderate lymphocytic infiltration [Table/Fig-2]. Dense lymphocytic infiltrate with germinal centers and few follicular cells (grade III) were noted in 10 (11.3%) patients [Table/Fig-3].

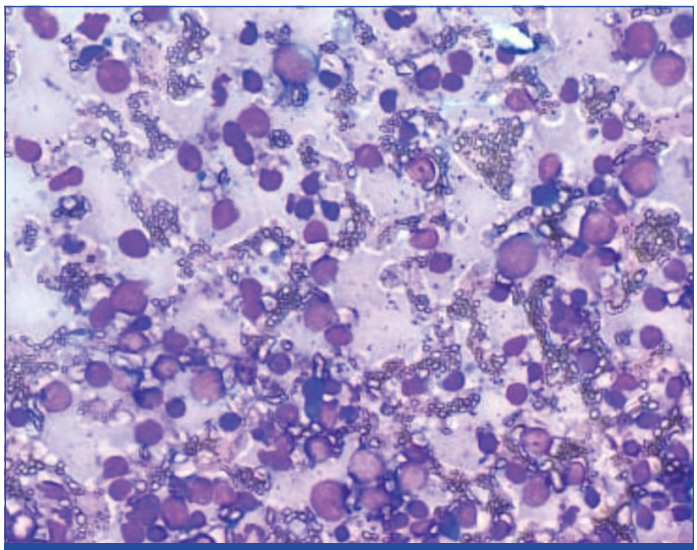


[Table/Fig-1]: Photomicroph showing grade I thyroiditis with lymphocytes infiltrating follicles (MGG, X400).
MGG: May grunwald-giemsa

Based on thyroid profile 58 (66%) patients had hypothyroidism, 23 (26.1%) were euthyroid and 7 (7.9%) had toxic features. Grade I thyroiditis was present in 48.3% (28/58) of hypothyroid patients while grade II was frequent among hyperthyroid (57.1%, 4/7) [Table/Fig-4]. Although grades of LT didn't significantly correlated with TSH levels (F=2.99, p=0.055) in all the groups but in hypothyroid group



[Table/Fig-2]: Grade II thyroiditis showing moderate lymphocytic infiltration with anisocytosis and hurthle cell change (MGG, 400x).



[Table/Fig-3]: Grade III thyroiditis showing dense lymphocytic infiltration with few follicular cells (MGG, 400x).

strong correlation was noted between grades of LT and TSH levels (r=0.28, p=0.029).

Hurthle cell change was seen in 45 cases [Table/Fig-5]. Only 36 cases showed plasma cells and most of these were patients with grade I thyroiditis. Giant cells and histiocytes were observed in 12 and 21 cases respectively [Table/Fig-6]. Fire flare was noted in 6 (6.8%) cases while background colloid was present in 27 (30.6%) cases.

Serological Correlation

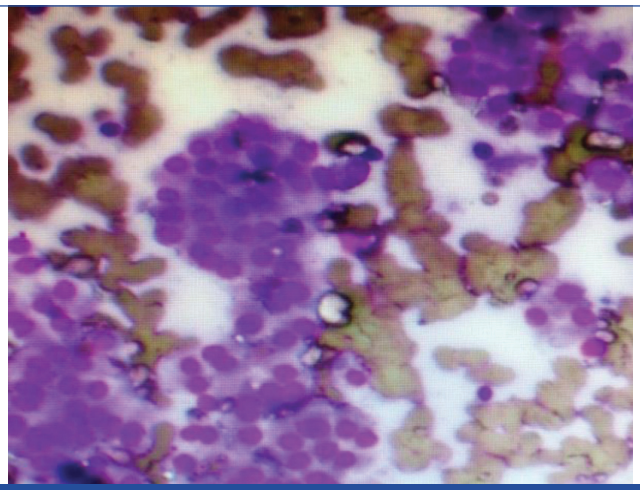
Elevated Anti-TPO antibody was present in 88.6% (78) cases. In grade I cases seropositivity was least i.e., 85% (34/40) while in grade III and grade II it was 90% (9/10) and 92.1% (35/38), respectively [Table/Fig-4]. Around 93% (54/58) of hypothyroid and 86.9% (20/23) of euthyroid patients had elevated ATPO [Table/Fig-7]. Elevated anti-TPO with an increased TSH was seen in 69.2% (54/78) of the cases, increase in anti-TPO with decreased TSH was seen in 5.1% (4/78) of the cases, while normal TSH with normal anti-TPO levels was noted in 30% (3/10) cases. The ATPO levels significantly correlated with cytological grades (p=0.004) and TSH level (r=-0.23, p=0.03) [Table/Fig-4,8].

Vitamin D Correlation

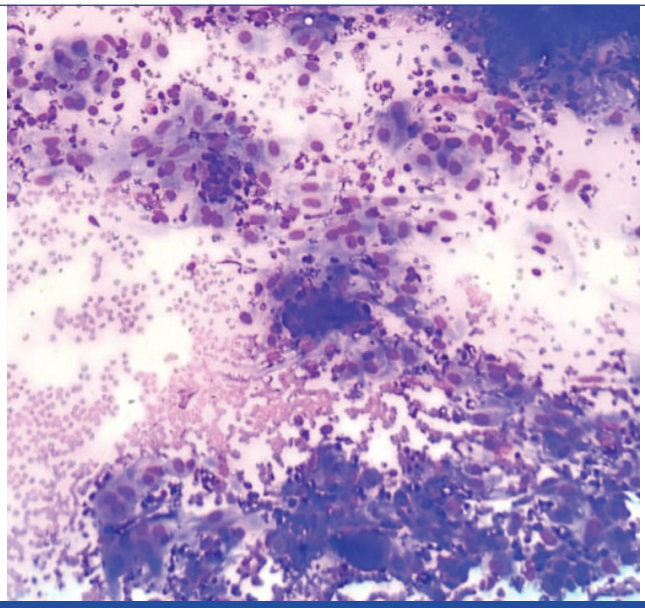
When correlated with the Vit D status, Vit D deficiency was observed in 72/88 (81.8%) with mean 13.4±8.94 ng/mL. Around 90% (9/10) of Grade III patients were Vit D deficient and had lowest mean value (7.8±4.9 ng/mL) followed by grade II patients (12.7±8.09 ng/mL) [Table/Fig-4]. On basis of thyroid functional status, lowest Vit D

TSH and cytological grades						
TSH	Grade I (n=40)	Grade II (n=38)	Grade III (n=10)	Mean±SD µIU/mL	F ratio	p-value
Hyperthyroid (n=7)	2	4	1	0.025±0.03	2.99	0.055
Euthyroid (n=23)	10	11	2	2.8±0.99		
Hypothyroid (n=58)	28	23	7	21.1±28.9		
Mean±SD	8.7±11.8	16.8±19.7	23.3±38.7	14.6±25.1		
ATPO and cytological grades						
ATPO	Grade I (n=40)	Grade II (n=38)	Grade III (n=10)	Mean±SD IU/mL	F ratio	p-value
Elevated (n=78)	34	35	9	201.1±91.2	8.53	0.004
Normal (n=10)	6	3	1	16.8±11.3		
Mean±SD	145.3±57.7	215.6±111.2	252.2±118.8	192.3±86.7		
Vit D and cytological grades						
Vit D	Grade I (n=40)	Grade II (n=38)	Grade III (n=10)	Mean±SD ng/mL	F ratio	p-value
Deficient (n=72)	31	32	9	9.6±3.6	4.12	0.019
Normal (n=16)	9	6	1	26.6±5.2		
Mean±SD	15.1±10.4	12.7±8.09	7.8±4.9	13.9±9.3		

[Table/Fig-4]: Comparison of cytological grades with different parameters.



[Table/Fig-5]: Grade II thyroiditis showing flat sheets of Hurthle cells with sparse lymphocytes in background (MGG, X400).



[Table/Fig-6]: Grade II thyroiditis showing the presence of Hurthle cells, epithelioid cells, giant cells, and anisonucleosis and increased number of lymphocytes (MGG, X100).

level was observed in hyperthyroid patients (9.9±5.6 ng/mL) while euthyroid patients had 16.5±9.2 ng/mL. The Vit D levels showed statistical significant negative correlation with thyroid functional state of patients (r=-0.29, p=0.15) as well as with cytological grades (p=0.019) [Table/Fig-4,8].

ATPO	Hypo	Euthyroid	Hyper	Total	χ^2	p-value
Elevated	54 (61.4%)	20 (22.7%)	4 (4.5%)	78 (88.6%)	8.87	0.012
Normal	4 (4.5%)	3 (3.4%)	3 (3.4%)	10 (11.4%)		
Total	58 (66%)	23 (26.1%)	7 (7.9%)	88 (100%)		
Vit D	**Hypo**	**Euthyroid**	**Hyper**	**Total**	χ^2	**p-value**
Deficient	52 (59.1%)	14 (15.9%)	6 (6.9%)	72 (81.9%)	9.25	0.009
Normal	6 (6.9%)	9 (10.2%)	1(1.01%)	16 (11.1%)		
Total	58 (66%)	23 (26.1%)	7(7.9%)	88 (100%)		

[Table/Fig-7]: Relationship of thyroid functional state with ATPO and Vit D levels.

Correlation between	r value	r^2	p-value
TSH and ATPO levels	0.23	0.052	0.03
TSH and VIT D	-0.29	0.084	0.015
VIT D and ATPO	-0.36	0.13	0.005

[Table/Fig-8]: Correlation of TSH with ATPO and Vit D levels.

DISCUSSION

The Vit D deficiency and thyroid diseases are increasingly common health problems in today's world. Most of the Indian studies have reported the prevalence of Vit D deficiency as high as 80-90% while LT to be between 7.6-15.3% [3,6,11]. Vitamin D which is important for bone and mineral homeostasis also plays a significant role as immunomodulator by inhibiting the activation of Th1, Th17 cells and production of proinflammatory cytokines (IL-2, IL-17 and interferon-γ) while enhancing anti-inflammatory Th2 cytokines (IL-3, IL-4, IL-5, and IL-10) production. The B cells proliferation and differentiation into plasma cell is also inhibited and B cells apoptosis is induced by Vit D [8,12]. This ability to promote immune tolerance by suppressing adaptive immune system seems beneficial for a number of autoimmune diseases [13]. Over past decade many studies could demonstrate an inverse relation between Vit D levels and development of autoimmune diseases especially autoimmune thyroiditis [1,12].

The LT is common polygenic disease characterised by diffuse goiter, production of thyroid-specific autoantibodies and shift of balance between Th1-Th2 immune response resulting in Th1 cell mediated thyrocyte destruction and thyroid dysfunction [6,14]. Based on the spectrum of injury, there is an initial transient phase of hyperthyroidism followed by hypothyroidism. Depending on stage of disease patients have different clinical features, hormonal status and thyroid autoantibodies levels. The FNAC is a basic and reliable diagnostic tool for patients of LT as cytological features are well defined. However very little is known about influence and correlation of Vit D deficiency with LT cytomorphological features which was the objective of this study.

Female patients constituted the majority with 82/88 (93.2%). The average age of patients was 34.4±12.9 years which ranged from 13 to 62 years and male patients had higher mean age 38.2±7.6 years at presentation which was in accordance to study by Bhatia A et al., Sood N and Nigam JS and Vanderpump MPJ et al., [4,5,15]. Diffuse thyromegaly was the most common presentation seen in 78.4% (69/88) cases followed by nodular presentation observed in 18.2% (16/88) of the patients while 3 (3.4%) cases had only pain. As opined by authors that in early stages of HT patients have nodular disease where as in later stages, with established clinical and hormonal changes they present with diffuse form [8]. Due to increasing awareness about thyroid diseases higher proportion of patients in present study had presented with early stage and nodular disease.

On the basis of thyroid functional status most of the patients (66%, 58) were hypothyroid including 10.2% (9) cases of subclinical Hypothyroidism (SCH). 88.6% (78/88) cases were seropositive with elevated Anti-TPO levels in which majority (61.5%, 54) had hypothyroidism [Table/Fig-2]. Seronegativity of 11.4% (10/88) patients was also explainable as it usually occurs in initial phase of disease due to localised immunodestruction before detectable positive serological findings [16,17]. These observations were in accordance with study of Sahoo N et al., [18]. Statistical correlation of ATPO levels and TSH levels was found to be significant (r=-0.23, p=0.03). This proposes that higher ATPO levels may be linked with hormonal derangement. Similar correlation was reported in earlier studies by Anila K et al., and Ahluwalia C et al., [6,19].

Thyroid smears of all 88 patients with cytological diagnosis of LT were further graded according to the criteria proposed by Bhatia A et al., [4]. In present study most of the cases belonged to grade I disease (40, 45.5%) while 38 (43.2%) had grade II thyroiditis. These results were comparable to study by Anila K et al., [6]. In present study, different cytological grades correlated significantly with thyroid hormonal status in hypothyroid group only (p<0.001) while hyperthyroid and euthyroid group did not correlate strongly. Some of earlier studies by Bhatia A et al., and Anila K et al., did not find correlation between thyroid functional status and cytological while Ahluwalia C et al., founded strong correlation between these parameters [4,6,19].

The Vit D deficiency was observed in 72 (81.8%) of cases. A 52 (59.1%) of them were hypothyroid followed by 14 (15.9%) euthyroid patients. Hyperthyroid patients had lowest Vit D levels (7.9%, 9.9±5.6 ng/mL). Similar results were earlier reported by Unal AD et al., [20]. Thyroid functional status significantly correlated with Vit D status (p=0.009) [Table/Fig-4]. On basis of cytological grades although total 44.4% (32) of Vit D deficient cases had grade II LT but highest prevalence (90%, 9/10) and lowest Vit D level (7.8±4.9 ng/mL) was noted in grade III. A 68/72 (94.4%) of Vit D deficient patients had elevated ATPO values. Strong negative statistically significant correlation between Vit D levels with ATPO was observed (r=-0.36, p<0.005) similar to what was reported in earlier studies [19]. In present study there was a significant correlation between Vit D levels and different cytological grades (p=0.019) which suggests that patients with lower levels of Vit D are likely to have higher grades of thyroiditis. As this study was first to do and no previous data on same is available, so more studies would be required for validation.

Cytomorphological Analysis

High lymphocyte-epithelial cell (L:E) ratio (≥2:1) is a common feature of LT. In present study smears of (21/58) hypothyroid patients showed higher L:E ratio in comparison to only two hyperthyroid cases which showed fewer lymphocytes along with prominent Hurthle cell change and more colloid. In Graves' Disease (GD) and Hashitoxicosis lymphocytic infiltration is known to be milder, so careful search for lymphocytes/lymphocytic infiltration is required [8,9]. In present study most of hyperthyroid cases, showed lesser L:E ratio, were seropositive and Vit D deficient. Although Sood N and Nigam JS had reported significant correlation of L:E ratio with ATPO levels [5]. In this study no significant correlation was observed between TSH, Vit D and ATPO levels with L:E ratio. In authors opinion this needs to be corroborated by larger studies.

As emphasised by Jayaram G et al., presence of plasma cells favours diagnosis of LT so is very helpful feature to look for in doubtful cases, especially in early stage or grade I of HT [7]. Plasma cells were seen in smears of 36 (40.9%) patients out of whom 22 were grade I thyroiditis. Most of them (27) were hypothyroid followed by (5) euthyroid and (4) hyperthyroid patients. The ATPO level was elevated in all and Vit D deficiency was noted in 33/36 patients. Statistical correlation of ATPO and Vit D status with plasma cells presence was found to be significant (p=0.002), (p=0.04), respectively (data not shown).

Cytological feature like Hurthle cell change with anisonucleosis and, plasma cells, histiocytes, and occasional giant cells were also noted in varying proportions. Hurthle cell change with anisonucleosis was noted in 45 cases; it was interesting to find that most of them had elevated ATPO and deficient Vit D levels (95% and 92%, respectively). Although these findings suggest that high ATPO and low Vit D levels are associated with Hurthle cell change as they were found statistically significant (p<0.05) but need more elaborate studies. Moreover, it is already documented that in early stages of LT before evident serological derangements, aspirates from hyperplastic nodule may predominantly comprise of Hurthle cells with absent lymphocytic infiltrate and sparse lymphocytes in background which raises the suspicion of Hurthle cell neoplasm [10]. Cytopathalogist should keep in mind that Hurthle cells in flat sheets favour thyroiditis while poorly organised, and poorly cohesive cell clusters favour neoplasia [9]. Incidentally, during present study in FNAC of one of our patients, who had presented with nodular disease, showed sheets of Hurthle cells with few lymphocytes in background and was reported as grade II thyroiditis. The patient's thyroid profile and ATPO levels were normal, however he had gross Vit D deficiency (<5 ng/mL).

Fire flare was noted in only six cases, three were hyperthyroid while three had high TSH. This suggests that fire flare on cytology does not reliably reflect hormonal status. Out of these four had grade II thyroiditis on cytology while grade I and grade III thyroiditis was observed in one each. All of them had elevated ATPO levels and Vit D deficiency.

As already known that in well established disease due to destruction of follicular epithelial cells, scanty or absent colloid is a feature but abundance of colloid does not rule out HT [9,19]. Moreover coexisting colloid goiter with LT is not rare, technique of aspiration and stage of disease too can influence the cytological picture. In present study colloid was noted in 27 (30.6%) cases, four out of them were hyperthyroid cases who showed coexisting follicular hyperplasia. Giant cells and histiocytes were observed in 12 (13.6%) and 21 (23.8%) cases, respectively. None of these significantly correlated with hormonal or serological parameters.

The FNAC is a very cost effective and highly sensitive method of diagnosing LT still it has certain pitfalls leading to diagnostic dilemma. Like in cases of nodular disease smears showing predominantly Hurthle cells or hyperplastic follicular cells with limited of lymphocytes in background or abundant colloid in background leading to likelihood of missing the diagnosis or florid lymphocytic infiltrate mistaken as low grade lymphoma. Data of present study showed that ATPO and Vit D levels significantly correlate with cytomorphological grades and certain cytomorphological features like with Hurthle cell change and presence of plasma cells. Moreover thyroid functional status significantly correlated with Vit D deficiency, ATPO levels and cytological grades of hypothyroid group only while euthyroid and hyperthyroid did not correlate. Thus cytopathalogist can avoid uncertainties in diagnosis by being aware of these interactions and overlapping features, and should always follow a multidisplinary approach with clinicopathological correlation [6,18].

Limitation(s)

Present study was limited by sample small size, little number of hyperthyroid patients. To our knowledge this was the first study to compare Vit D deficiency with cytomorphological features of LT. Further studies with larger sample size and control group may be required for corroboration and definite results.

CONCLUSION(S)

The Vit D deficiency has been associated with increased risk of autoimmune thyroiditis onset and/or its high activity while deranged thyroid functional and serological parameters are result of disease activity itself. The Vit D and ATPO levels have shown to correlate significantly with different cytomorphological features, cytological

grades and TSH levels suggesting these two greatly influence the cytological picture. Hence, it's recommended to be aware of these interactions and adopt integrated approach while interpreting cytology for definitive diagnosis.

REFERENCES

[1] Makariou S, Liberopoulos EN, Elisaf M, Challa A. Novel roles of vitamin D in disease: What is new in 2011? Eur J Intern Med. 2011;22:355-62.
[2] Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266-81. Doi: 10.1056/NEJMra070553.
[3] Marwaha RK, Garg MK, Nijhavan VS, Dham DN, Dubey R, Amberdar V, et al. Prevalence of chronic lymphocytic thyroiditis in adolescent girls. J Assoc Physicians India. 1998;46:606-08.
[4] 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. Cytojournal. 2007;4:10.
[5] Sood N, Nigam JS. Correlation of fine needle aspiration cytology findings with thyroid function test in cases of lymphocytic thyroiditis. J Thyroid Res. 2014;2014:430510.
[6] Anila K, Nayak N, Jayasree K. Cytomorphologic spectrum of lymphocytic thyroiditis and correlation between cytological grading and biochemical parameters. J Cytol. 2016;33:145-49.
[7] Jayaram G, Iyengar KR, Sthaneshwar P, Hayati JN. Hashimoto's thyroiditis–A Malaysian perspective. J Cytol. 2007;24:119-24.
[8] Klecha AJ, Barreiro Arcos ML, Frick L, Genaro AM, Cremaschi G. Immune-endocrine interactions in autoimmune thyroid diseases. Neuroimmunomodulation. 2008;15:68-75.
[9] Orell SR, Sterrett GF. Orell & Sterrett's Fine Needle Aspiration Cytology. 5th ed. New Delhi: RELX India Private Limited; 2012.
[10] Ali SZ, Cibas ES. The Bethesda System for Reporting Thyroid Cytopathology. Definitions, Criteria and Explanatory Notes. 2nd ed. Switzerland: Springer; 2018
[11] Aparna P, Muthathal S, Nongkynrih B, Gupta SK. Vitamin D deficiency in India. J Family Med Prim Care. 2018;7(2):324-30.
[12] Beke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: Modulator of the immune system. Curr Opin Pharmacol. 2010;10:482-96.
[13] Murdaca G, Tonacci A, Negrini S, Greco M, Borro M, Puppo F, et al. Emerging role of vitamin D in autoimmune diseases: An update on evidence and therapeutic implications. Autoimmun Rev. 2019;18(9):102350.
[14] Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients. 2013;5:2502-21.
[15] Vanderpump MPJ, Tunbrldge WMG, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: A twenty-year follow-up of the Whickham Survey. Clin Endocrinol. 1995;43(1):55-68.
[16] Amino N. Thyroid directed antibodies. In: Ingbar SH, Braverman LE, editors. Werner's the Thyroid– A Fundamental and Clinical Text. Philadelphia: JB Lippincott Co; 1986. Pp. 546-59.
[17] Saraf SR, Gadgil NM, Yadav S, Kalgutar AD. Importance of combined approach of investigations for detection of asymptomatic Hashimoto Thyroiditis in early stage. J Lab Physicians. 2018;10:294-98.
[18] Sahoo N, Naik S, Mohanty P, Sahoo PN, Das P. The cytomorphological spectrum of Hashimoto thyroiditis and its correlation with serological parameters: A study in the coastal region. J NTR Univ Health Sci. 2020;9:25-31.
[19] Ahluwalia C, Ranga S, Agarwal S, Kansra U. Study of cytomorphological features of Hashimoto's thyroiditis and their correlation with serological findings. Med Int Med. 2015;2(12):832-36.
[20] Unal AD, Tarcin O, Parildar H, Cigerli O, Eroglu H, Demirag NG. Vitamin D deficiency is related to thyroid antibodies in autoimmune thyroiditis. Cent Eur J Immunol. 2014;39(4):493-97.

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