Original Research Article

Autoimmune thyroiditis - Correlation of cytomorphological features and AMA titre

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Abstract

Background: Thyroiditis is the second most common thyroid lesion next to endemic goitre diagnosed on FNA in iodine (I2) deficient areas.
Aim: This study was carried out to study correlation between various cytomorphological features with anti-thyroid antibodies in cases of autoimmune thyroiditis diagnosed on FNAC.
Materials and methods: This was a retrospective study carried out in a tertiary care teaching hospital. 150 cases diagnosed as autoimmune thyroiditis in a two year period from January 2010 to December 2011 formed the study group. The cytological findings and AMA tires were noted from the medical record available with the patient and also from Endocrinology department records.
Results: Incidence of autoimmune thyroiditis was found to be 13.4%. Majority of the patients were females (96.7%), 53.3% of cases were seen in 21-40 years age group. In 97 patients anti-microsomal antibody titre (AMA) was available, 83 were positive i.e.85.6% positivity. Association between grade of lymphocytes, grade of thyroiditis and high L:E ratio with AMA titre was found to be statistically significant. Of the cytologically diagnosed cases of autoimmune thyroiditis, 14.4% cases showed AMA negativity. Thus FNAC remains the gold standard for the diagnosis.
Conclusion: Grade of lymphocyte infiltration and grade of thyroiditis correlated well with AMA positivity. Association between high L:E ratio and AMA titre was found to be statistically significant.

Key words

Autoimmune thyroiditis, Cytomorphological features, Anti-thyroid antibodies, Anti-microsomal antibody titre.

Introduction

Thyroiditis is the second most common thyroid lesion next to endemic goitre diagnosed on FNA in iodine (I2) deficient areas [1].

Fine needle aspiration cytology (FNAC) is a well-known safe, cost-effective diagnostic procedure. It can be performed as a simple office procedure, with ordinary syringe and needle, without any known significant complications [2]. The procedure in most instances is simple, inexpensive, safe and quick [3]. The ease and simplicity of the procedure and the diagnostic accuracy comparable to other invasive procedures have contributed greatly to the wide application of FNAC in thyroid. .

This study was carried out to correlate various cytomorphological features with anti-thyroid antibodies in cytologically diagnosed cases of autoimmune thyroiditis.

Autoimmune thyroiditis

Hashimoto's / chronic lymphocytic thyroiditis are a part of the spectrum of autoimmune thyroid diseases. At one end of this spectrum is Hashimoto's thyroiditis, which usually presents as hypothyroidism and at other end is Grave's disease [4]. In favor of this interpretation is the existence of cases sharing features of both disease (sometimes designated as Hashitoxicosis), suggesting that one may evolve into another [5, 6].

Some investigators consider autoimmune thyroiditis as a histological diagnosis that may be subdivided into lymphocytic thyroiditis if only lymphocytic infiltration is present and as Hashimoto's thyroiditis if atrophy and oncocytic change of the epithelium is seen [4]. Many others use chronic lymphocytic thyroiditis and Hashimoto's thyroiditis as synonymous terms [7, 8].

Clinically, chronic autoimmune thyroiditis is said to have two forms – A goitrous form which is often referred to as Hashimoto's thyroiditis and an atrophic form called atrophic thyroiditis [9].

During the past few decades there has been a reported increase in the incidence of Hashimoto's thyroiditis, which could be attributed to newer diagnostic modalities such as needle biopsies and serological tests, and their increased sensitivity when compared to the older methods [10].

Autoimmune thyroiditis is about 15-20 times more common in women than in men and frequently involves people between the ages of 30 and 50 years of age.

Chronic autoimmune thyroiditis is rare in children younger than five years of age, but it does occur in children and accounts for 40 percent or more of cases of goiter in adolescents [11].

The prevalence of positive tests for thyroid antibodies increases with age, with frequencies as high as 33 percent in women 70 years old or older.

The etiology of autoimmune thyroiditis is considered to be multi-factorial, involving the interplay of various environmental and genetic factors. The pathogenesis of Hashimoto's thyroiditis is a complex multistep process which involves various genetic, environmental and immunological factors [12].

Laboratory investigations

Autoimmune thyroid disease is detected most easily by measuring circulating antibody against thyroid peroxidase (TPO) and Thyroglobulin (Tg) [13]. Thyroid peroxidase (TPO) is a key enzyme in the synthesis of thyroid hormone and is a major antigen corresponding to thyroid anti-microsomal autoantibodies [14]. Highly sensitive assays of TPOAb using radioimmunoassays and enzyme immunoassays have been developed following a hemagglutination assay technique [15].

There is a good correlation between the degree of lymphocytic infiltration of the thyroid gland and the titre of TPOAb [16].

For cases in which Hashimoto's thyroiditis is suspected clinically but antibody titres are not elevated, fine needle aspiration (FNA) and cytological examination continue to play a defining role in establishing the diagnosis [1, 17].

Cytology in Autoimmune thyroiditis

Cytology is believed to be the gold standard in the diagnosis of thyroiditis. The cytomorphologic features of autoimmune thyroiditis may be described as follows

Acute lymphocytic thyroiditis:

It is viewed as the incipient stage of Hashimoto's thyroiditis or juvenile autoimmune thyroiditis because it is observed in children, young patients with euthyroidism and discrete glandular enlargement [18]. Moreover in some patients serum antibody titres are low or normal [19]. The aspiration contains little colloid, numerous lymphoid cells. Hurthle cells are very sporadic [20]. The lymphoid cells correspond mainly to mature lymphocytes but stimulated lymphocytes and plasma cells can be seen. The lymphocytes often have artifacts produced by extension [21].

Hypertrophic Lymphocytic Thyroiditis

This florid form, representing the classical Hashimoto's disease, is observed in women with hypofunctional goitre (unilateral or diffuse) often accompanied by high serum antibody levels [22]. On FNA variable amount of bloody fluid is aspirated, scanty colloid, abundant cellularity either lymphoid / epithelial, mature lymphocytes, plasma cells, centrifollicular lymphoid cells and macrophages are observed. Variable numbers of oncocytic cells are observed.

Atrophic Lymphocytic Thyroiditis

Patient present with hypothyroidism associated with fibrous goitre [23], on fine needle aspiration, little material is aspirated composed of fibroblasts, lymphocytes, follicular cells and oncocytic cells [24].

Materials and methods

This was a retrospective study carried out in a tertiary care teaching hospital, Seth G S Government Medical College, Mumbai, Maharashtra, India. 150 cases diagnosed as chronic lymphocytic thyroiditis and mixed thyroiditis in a two year period from January 2010 to December 2011 formed the study group.

A case was put in the category of mixed thyroiditis if it showed Hurthle cells while, in the absence of Hurthle cells a diagnosis of chronic lymphocytic thyroiditis was given. Both these categories represent autoimmune thyroiditis in our study.

The clinical history, other significant findings, cytological findings and AMA tires were noted from the medical record available with the patient and also from Endocrinology department records.

Anti-thyroid microsomal antibodies were measured by Hemagglutination techniques, titre $> 1:20^2$ were considered positive.

FNACs had been performed using a 24 gauge sharp disposable needle and 10 ml disposable syringes using both aspiration and non-aspiration techniques. Standard procedure was followed and with each pass the smears obtained were equally distributed. Smears were air dried and alcohol fixed. The air dried smears were stained with Geimsa stain and Papanicolaou staining was done on the fixed smears.

All the smears were reviewed and the following parameters were studied.

Amount of lymphocytic infiltration [Number of lymphocytes/high power field (hpf)] [27]

Based on the number of lymphocytes per hpf lymphocytic infiltration was graded as.

Grade I: <10 lymphocytes/hpf,

Grade II: 11-20 lymphocytes/ hpf,

Grade III: >21 lymphocytes/hpf

Presence of follicular center cells

Presence of Oxyphil cells/ Hurthel cells
Presence of follicular destruction

Thyroiditis was graded as follows using the criteria proposed by Bhatia, et al. [8]
Grade 0: No lymphoid cells.
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.

Ratio of lymphocytes to epithelial cells recorded where follicular epithelium as well as background epithelium were represented in the smears [28]. Ratio >2:1 is considered high.

Eosinophils – number, infiltration of TFC clusters by eosinophils
Amount and type of colloid.
Presence of granuloma, giant cells.

The grade of lymphocytic infiltration, grade of thyroiditis and L:E ratio were correlated with the AMA levels.

Statistical analysis was done using chi- square test; Fisher's exact test was used where applicable. A p value of ≤ 0.05 was considered statistically significant.

Results

In 2 year period i.e. from January 2010 to December 2011, total 7,756 FNACs were performed and out of these 1113 were thyroid FNACs. Thyroid aspirations accounted for 14.4% of all FNAs (**Table – 1**).

152 cases of thyroiditis were identified, of which 150 cases were chronic lymphocytic thyroiditis/ mixed thyroiditis and 2 were subacute thyroiditis. Autoimmune thyroiditis was thus diagnosed in 13.4% of thyroid aspirates.

Table – 1: Total number of thyroid FNACs in retrospective 2 years among total FNACs performed.

	Number	**%**
Total FNACs	7756	100
Thyroid FNACs	1113	14.4

Table – 2: Distribution of cases of autoimmune thyroiditis (n=150 cases).

Type of thyroiditis	**No of cases**	**%**
Mixed thyroiditis	103	68.7
Chronic lymphocytic thyroiditis	47	31.33

Table - 3: Age and sex wise distribution of autoimmune thyroiditis cases (n=150).

Age range (Years)	**Male**	**Female**	**Total**
0-12	-	06	06
13-20	03	22	25
21-30	01	49	50
31-40	-	30	30
41-50	-	21	21
51-60	01	15	16
61 – 70	-	02	02
Total	05	145	150

Table - 4: Anti microsomal antibody titre (AMA) (n=97).

AMA status	**Number**	**%**
AMA result available	97	100
AMA positive	83	85.6
AMA negative	14	14.4

Table - 5: Correlation of AMA titre and type of autoimmune thyroiditis (n=97).

AMA	**Type of thyroiditis**		**Total**
	Mixed thyroiditis	**Chronic lymphocytic thyroiditis**	
Positive	48	35	83
Negative	06	08	14

Autoimmune thyroiditis was seen in 13.4% of all thyroid FNAs. Mixed thyroiditis seen in 68.7% and chronic lymphocytic thyroiditis in 31.33% cases (**Table – 2**).

Table – 6: Cytomorphological features (n=150).

Cytomorphological features			**Number of cases**	**Percentage**
Number of lymphocytes	Grade I		13	8.7
	Grade II		57	38
	Grade III		80	53.3
Grade of thyroiditis	No. of lymphocytes	Mild	13	8.7
		Moderate	57	38
		Severe	80	53.3
	TFC destruction		103	68.6
	Hurthle cells		103	68.6
	GCC		70	46.6
	Giant cells		44	29.3
	Grade	I	07	4.6
		II	63	42
		III	80	53.3
Eosinophils	Infiltrate of TFC		13	8.6
	Clusters		12	08
Granulomas			13	8.6
L:E Ratios	High		101	67.3
	Low		49	32.6
Colloid	Thick and thin		77	51.3
	Scanty thick		69	46
	No colloid		04	2.6

Table – 7: Correlation between grade of lymphocytes and AMA titre (n=97).

Grade of lymphocyte	**AMA Titre (n=97)**		**Total**
	Positive	**Negative**	
Grade I (n=13)	1	1	2
Grade II (n=56)	19	9	28
Grade III(n=81)	63	04	67

Table - 8: Association between grade of thyroiditis and AMA titre.

Grade of thyroiditis	**AMA available n = 97**	**AMA Positive n = 83**	**AMA Negative n = 14**	**AMA Not available**
Grade I	2	01	01	5
Grade II	29	20	09	34
Grade III	66	62	04	14

Majority of the patients were females (96.7%), only 5 male patients (3.3%) were seen. M:F ratio was 1:29. 53.3% of cases were seen in 21-40 years of age group, maximum number of cases seen in the 3rd decade (33.4%). The youngest patient was a 7 year old girl while the oldest patient was a 63 year old female (**Table – 3**).

AMA titre was not available in 53 cases. 85.6% cases with AMA titre available showed AMA positivity (**Table – 4**). Of the 103 patients of mixed thyroiditis, AMA titre of 54 patients was available, 48 were positive and 6 had a negative AMA titre (**Table – 5**). Out of 47 patients of chronic lymphocytic thyroiditis, AMA titre of 43 patients was available, of which 35 were positive and 8 had a negative AMA titre. Thus, there was no significant difference in the AMA positivity between cases of mixed thyroiditis (88%) versus Chronic lymphocytic thyroidits (82%). The cases were studied as per the various parameters proposed. The number of lymphocytes was graded independently and they also formed one of the parameters for grading thyroiditis.

Granulomas were seen in 13 cases (8.6%) and giant cells were noted in 44 cases (29.3%). 4 cases did not show any colloid while the colloid was scanty and thick in 69 cases (46%). Both thick and scanty thin colloid was present in 77 cases. Abundant colloid was not seen in any of the cases (**Table – 6**).

Grading of lymphocytes

53.3% cases showed grade III lymphocytes i.e. more than or equal to 21 lymphocytes per high power field while 9 cases showed less than 10 lymphocytes per hpf (**Table – 7**).

7 patients (2%) patients had grade I thyroiditis while 80 patients showed grade III thyroiditis (**Table – 8**). 62 / 83 cases with AMA positivity showed grade III thyroiditis.

Association between grade of thyroiditis and AMA titre showed that as the grade of thyroiditis increased from Grade I to grade III, the positive AMA status increased from 50% to 94% respectively, with a intermediate positive % status (69%) among Grade II cases. This indicates that the AMA positivity is proportional to the grade of thyroiditis. The correlation between grade and AMA positivity was statistically significant (p-value=0.0013).

L:E ratio was high in 101 (67.3%) cases ranging from 2:1 to 10:1 (**Table – 9**).

Table – 9: Lymphocyte to epithelial cell ratio (n=150).

L:E Ratio	No of cases	Percentage
High	101	67.3%
Low	49	32.7%
Total	150	100%

AMA titre was available in 80 cases with a high LE ratio, of these 75 cases (93.7%) showed AMA positivity (**Table – 10**).

Association between high L:E ratio and AMA titre was found to be statistically significant (p-value=0.0001).

Table - 10: Comparison between L:E Ratio and AMA titre (n=97).

L:E ratio	AMA titre	
	Positive	Negative
High	75	5
Low	8	9

Discussion

Incidence

The incidence of autoimmune thyroiditis in present study was 13.4%. Three large studies that analysed thyroid aspirates, namely those by Kapila, et al. [23], Gagneten, et al. [27] and Staii, et al. [28], have found an incidence of 14.3, 13.4 and 13.4% respectively. Our incidence of autoimmune thyroiditis was concordant with these large studies.

Age and sex wise distribution

Our patients were also predominantly females (96.7%), M:F ratio 1:29, but most of our cases were in the age group of 21-40. The age in our study is in concordance with the study by Bhatia, et al. [8] and Kapila, et al. [23], carried out in Indian patients. Disparity between the ages in the Western and Indian literature may be explained by the theory put forth by Kumar, et al. [4] wherein they have proposed that Hashimoto's thyroiditis occurs earlier in Iodine deficient areas such as ours, compared to Iodine sufficient areas.

Children and young adults were also affected; there were six cases between 0- 12 years of age and 25 cases between the age of 13-20 years. Most of these presented as diffuse goiter. Marwaha, et al. [29] have proposed that chronic lymphocytic thyroiditis must be ruled out in all children presenting with a firm goitre as only 20.5% of their patients had clinical symptoms.

Good correlation was seen between the cytologic diagnosis of autoimmune thyroiditis and serum anti microsomal antibody levels. In 53/150 cases AMA results were not available. Serum AMA titres were elevated in 85.5% (83 out of 97) and negative in 14.5% (14 out of 93) of our patients whose AMA was available, which is concordant

to Guntekunst, et al. [30] and higher than other published reports like Poropatich, et al. [31] (52%), Jayram, et al. [32] (62.5%) and 65.1% cases in the study by Bhatia, et al. [8].

Cytological parameters

Cytological parameters as seen in our material are summarized in **Table – 6**. Lymphocytes form an important cytomorphological feature and were found in all i.e. 100% of proven cases.

Grading of lymphocytes

The number of lymphocytes per high-power field was counted and correlated with AMA titre. The grading of lymphocytes was done as grade 1 (<10/HPF) which was seen in 13 cases, grade 2 (11-20/HPF) found in 56 cases, and grade 3 (>/=21/HPF) found in 81 cases.

63 / 83 (76%) cases with AMA positivity showed grade III lymphocytes. The grade of lymphocytes correlates with anti-microsomal antibody (AMA) positivity in our study.

Association between Grade of Lymphocyte and AMA titre showed that as the grade of Lymphocyte increased from Grade I to grade III, the positive AMA status increased from 50% to 94% respectively, with intermediate positive % status (67.9%) among Grade II cases. This indicates that grade of lymphocytic infiltration is proportional to AMA. The association of grade and AMA positivity was statistically significant (p-value=0.0009).

Grading of thyroiditis

In this study grading was carried out on FNAC smears by applying criteria devised by Bhatia, et al. [8]. We categorized our 150 cases into grade I, grade II and grade III and correlated with Anti-microsomal antibody (AMA), thyroid status and other cytomorphological features.

7 (4.6%) patients had mild lymphocytic infiltration of the gland and were graded as Grade I thyroiditis. 63 (42%) patients had grade II disease characterized by mild to moderate degree of infiltrate with evidence of follicular destruction, Hurthle cell change, giant cells etc. Grade III thyroiditis was noted in 80 (53.3%) patients who showed dense infiltrates with germinal centre cells, very few follicular cells left.

Association between grade of thyroiditis and AMA titre showed that as the grade of thyroiditis increased from Grade I to grade III, the positive AMA status increased from 50% to 94% respectively. This indicates that the AMA positivity is proportional to the grade of thyroiditis. The correlation between grade and AMA positivity was statistically significant (p-value=0.0013). Grade of thyroiditis correlated poorly with AMA in the study by Bhatia, et al. [8]. The authors have cited various reasons like dilution by blood, technical issues with the procedure itself and sampling errors as the cause for poor correlation in their study.

Colloid

Absent or scanty thick colloid is a usual feature of Hashimoto's thyroiditis, as it is associated with the destruction of follicles in the long run. However various authors like Poropatich, et al. [31] and Nguyen, et al. [33] have emphasized the presence of colloid in Hashimoto's thyroiditis on FNAC. This finding was not encountered in our cases.

Eosinophils

We found eosinophils in 14.6% cases and infiltration of thyroid follicular cell clusters was seen in 8.6% cases**.** Singh, et al. [34] have also reported eosinophils in 14% cases.

Thyroid follicle cell (TFC) destruction was seen in 103 cases (68.6%) cases. 47 (31.3%) cases showed mild lymphocytic infiltration of a few thyroid follicular cell clusters without destruction of thyroid follicular cell clusters. 7 of these were of grade I thyroiditis while 40 cases were of grade II thyroiditis.70 /80 cases of grade III thyroiditis showed thyroid follicular destruction. Association of thyroid follicle destruction and grade III thyroiditis was found significant (p-0.003).

Hurthle cells were observed in 103 (68.6%) cases while in 47 cases Hurthle cells were absent. Similar results were obtained by Singh, et al. [34].

Germinal centre cells

70 cases (46.6%) showed the presence of germinal centre cells. 62 of these (88.5%) belonged to the category of grade III thyroiditis. Poropatich, et al. [31] found similar findings.

Giant cells were present in 29.3% of our cases. Jayram, et al. [32] reported giant cells in 33% cases and granuloma in 8% cases. In present study Granulomas were seen in13 (8.6%) cases.

L: E Ratio

L:E ratio is characteristically high in HT, ranging from 2:1 to 10:1 with smear cytology in florid cases often mimics a reactive lymph node [26]. Lymphoid: epithelial ratio was graded as 'low' and 'high' depending on the relative proportion of lymphoid and epithelial components [26]. In the present study, we found a high L:E ratio in 101 (67.3%) of the patients ranging from 2:1 to 10:1. Most of these patients had grade II or III thyroiditis, where the lymphoid population dominated the epithelial component**.** Our findings of a high L:E ratio are in accordance with those of Friedman, et al. [36], Jayram, et al. [32], Jayram, et al. [26] and Kini, et al. [35] In the present study anti-thyroid antibodies showed a statistically significant correlation with high L:E ratio. Similar correlation was also seen by Singh, et al. [34].

Conclusion

Of the cytologically diagnosed cases of autoimmune thyroiditis, 14.4% cases showed AMA negativity. Thus FNAC remains the gold standard for the diagnosis. Lymphocytes, germinal center cells, thyroid follicular destruction and Hurthle cells form important cytological features, while giant cells, eosinophils, granulomas were other cytomorphologic features in the diagnosis of autoimmune thyroiditis. Grade of lymphocyte infiltration and grade of thyroiditis correlated well with AMA positivity. Association between high L:E ratio and AMA titre was found to be statistically significant

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