Original Research Article

Autoimmune thyroiditis – Correlation between thyroid hormone status 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. This study was carried out to study correlation between thyroid hormone status with anti-thyroid antibodies in cases of autoimmune thyroiditis diagnosed on FNAC.

Aim: To correlate thyroid hormone status with anti-thyroid antibodies in cytologically diagnosed cases of autoimmune thyroiditis.

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 clinical history, TFT, 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 the age group 21-40 years age group. Of the patients with autoimmune thyroiditis, 110(73.3%) patients were euthyroid while 32 (21.3%) patients were hypothyroid at the time of FNAC. Only 8(5.3%) patients showed evidence of hyperthyroidism. 8% patients showed subclinical hypothyroidism. In 97 patients anti-microsomal antibody titre (AMA) was available, 83 were positive i.e.85.6% positivity. Of the cytologically diagnosed cases of autoimmune thyroiditis, 14.4% cases showed AMA negativity. Thus FNAC remains the gold standard for the diagnosis.

Conclusion: Autoimmune thyroiditis was seen more commonly in females, majority cases were seen in age group of 21-40 years. Euthyroid autoimmune thyroiditis was common in our study. Anti-microsomal antibody titre (AMA) was available in 97 cases, out of which 83 were positive i.e.85.6% positivity. Of the cytologically diagnosed cases of autoimmune thyroiditis, 14.4% cases showed AMA

negativity. Thus FNAC remains the gold standard for the diagnosis in subjects with a clinical diagnosis of Hashimoto's thyroiditis and negative antibody results.

Key words

Autoimmune thyroiditis, AMA, TFT.

Introduction

Autoimmune thyroiditis

There is no internationally accepted classification of autoimmune thyroid diseases. 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 [1]. In favour of this interpretation is the existence of cases sharing features of both disease (sometimes designated as Hashitoxicosis), suggesting that one may evolve into another [2, 3].

Some investigators consider autoimmune thyroiditis as a histologic diagnosis that may be subdivided into lymphocytic thyroiditis if only lymphocytic infiltration is present and as Hashimotos thyroiditis if atrophy and oncocytic change of the epithelium is seen [1]. Many others use chronic lymphocytic thyroiditis and Hashimoto's thyroiditis as synonymous terms [4, 5].

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 [6].

Grave's disease – diffuse goiter with hyperthyroidism, ophthalmopathy or both is thus a related autoimmune disease but not a form of autoimmune thyroiditis.

Hashimoto's thyroiditis was first described in 1912 by Dr. Hakuru Hashimoto. Based on the histological findings, Hashimoto originally used the term "Struma Lymphomatosa." Over the years, this disease has been called by several names including lymphocytic thyroiditis, autoimmune thyroiditis, chronic thyroiditis, and lymphadenoid goiter [7].

Incidence and distribution of the disease

The prevalence of autoimmune thyroiditis reported in studies varies with the criteria for diagnosis, the decade when the study was performed, and the patients studied.

Diagnostic criteria have included a positive test for thyroid autoantibodies in serum, an elevated serum thyrotropin concentration, and the presence of lymphocytic infiltration of the thyroid at autopsy. 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 [8].

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 [9].

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.

Etiology and Pathogenesis

The etiology of autoimmune thyroiditis is considered to be multifactorial, 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 [10]. Loss of immune tolerance to normal thyroid cells leads to production of antibodies directed against thyroid tissue, which causes the destruction of the thyroid gland. The initial inflammatory changes in the disease process are triggered when genetically predisposed individuals are exposed to the above mentioned environmental factors. The major histocompatibility complex (MHC) class 2 antigen presenting cells, which include dendritic cells and macrophages, invade the thyroid gland after the initial inflammatory process. These cells present the autoantigen components of the thyroid gland to the immune system for processing. Among the myriad of potential auto-antigens, thyroglobulin, the main protein produced in thyroid tissue, is believed to play a central role in the pathogenesis of this disease [11]. The thyroglobulin protein has been reported to have approximately 40 different types of epitopes, which play a vital role in the pathogenesis of the disease [12]. In contrast to the epitope recognition pattern of normal individuals, the epitope recognition pattern of the antibodies in autoimmune thyroid disease is altered triggering immune and inflammatory processes [13]. Thyroid peroxide, an enzyme that catalyzes the oxidation of iodine, also plays a significant role as an autoantigen in the disease pathogenesis. Moreover, 180 different types of thyroid peroxide antibodies have been identified, thus far. Studies have confirmed that even though antibodies against thyrotropin receptor and sodium iodide symporter have been detected in patients with autoimmune thyroid disease, they do not play a significant role in the pathogenesis of this condition.

The major step in the pathogenesis is the formation of autoreactive cells directed against the thyroid gland, which could result from defects in central tolerance or defects in the peripheral tolerance. Loss of immune tolerance has been associated with genetically determined immune defects or with the lack of regulatory T-cells which impose the suppressive function [14]. This is followed by formation, clonal expansion, and maturation of self-reactive T-lymphocytes and B-lymphocytes in the draining lymph nodes.

This step is then followed by a central phase of autoimmunity, characterized by uncontrolled production of self-reactive cells and autoantibodies in response to the presented antigens. This process initially occurs in the lymph nodes but as the disease progresses the production process shifts to the thyroid gland where the development of lymphoid tissue follows. The stimulated B-lymphocytes produce anti-thyroglobulin (TGAB) and anti-thyroid peroxide (ATPO) antibodies which are directed against thyroid cells. The autoreactive T-cells, which are produced in the disease process, infiltrate the thyroid gland and mediate destruction through cytotoxicity with the aid of CD+8 cells. The macrophages which are stimulated in this process produce numerous cytokines which, along with antibodies, initiate the process of tissue destruction via apoptosis.

As a final step in the process, caspases, which are self-activated through proteolytic cleavage, induce enzymes which are directly involved in the destruction of thyroid gland. In a normal thyroid gland, the production of new cells and the destruction of old cells are tightly regulated so that a constant proportion of functioning cells is always present. During the course of the disease, the control over destruction of cells in the thyroid gland is lost.

Genetic susceptibility is one of the factors that plays a vital role in deregulation of the regular destructive mechanisms in the thyroid gland. Several other triggers which have an influence on the expression of Bcl-2, the apoptosis inhibitor, or Fasl membrane ligand also are crucial in the initiation of the apoptosis process [15]. Thyroid cells in tissue affected with Hashimoto's thyroiditis, when compared to normal thyroid

cells, are capable of producing more Fasl proteins leading to an increased tempo of apoptosis [16]. The severity of the disease and the clinical outcome are determined by the rate at which apoptosis occurs in the thyroid gland. Expression of these proteins has direct correlation to the severity of the disease and as the rate of apoptosis increases, the mass of hormonally-active thyroid tissue decreases resulting in diminished production of thyroid hormones and more significant disease manifestations.

Clinical manifestations

Hashimoto's thyroiditis has a highly variable clinical presentation. Only about 20% of the patients exhibit signs and symptoms of mild hypothyroidism at initial presentation.

The symptoms of Hashimoto's thyroiditis are predominantly due to decreased production of thyroid hormone, which occurs as a result of destruction of thyroid tissue, ultimately leading to decreased metabolism. Indeed, most symptoms are not manifested in the early stages of the disease; as the disease advances and the degree of hypothyroidism increases, the symptoms become more evident. The decreased production of thyroid hormone adversely affects various major organ systems. Dysfunction of the cardiovascular system is manifested as bradycardia, while nervous system dysfunction manifests as slowed speech and delayed reflexes. Gastrointestinal symptoms include constipation, increased bile reflux and ascites. When the metabolic rate drops to a critical level, a life threatening emergency called myxedema coma occurs. Myxedema is usually characterized by hypothermia, altered sensorium and severe bradycardia. In severely hypothyroid Individuals, triggers such as stress, infection, surgery and traumatic injuries may also predispose to the development of myxedema.

In contrast to hypothyroid patients, patients in a euthyroid state do not experience any symptoms or exhibit any signs of the disease, and in most cases the diagnosis is incidental. Moreover, some individuals may not present with any clinical features except an enlarged thyroid gland and the diagnosis is made by investigating the goitre. The goitre, by itself, can cause cosmetic disfigurement in its initial stages and as its size increases, it can lead to pressure symptoms including pain in the neck, dysphagia, and dyspnea in some cases. Furthermore, a rapid growth in the goitre is sometimes noted, which may arouse suspicion for a tumour. Tumours of the thyroid gland, which sometimes arise in the background of Hashimoto's thyroiditis, usually manifest as solitary or multiple nodules typically discovered incidentally during a regular physical examination.

Though extremely rare in children, Hashimoto's thyroiditis can lead to detrimental effects on growth and physical maturation. Moreover, short stature and mental retardation are the features which are most commonly observed in children suffering from Hashimoto's thyroiditis. In addition to the symptoms of hypothyroidism, people suffering from Hashimoto's thyroiditis sometimes experience symptoms due to other autoimmune diseases. Muscle pain is present in 25.5% of patients with Hashimoto's thyroiditis.

Rheumatic manifestations in autoimmune thyroiditis are reported to be ten times more frequent when compared to non-autoimmune thyroiditis [17]. Furthermore, the initial presentation can sometimes be very subtle. For instance, occasionally, irritability, depression, confusion, and fatigue have been reported as initial complaints in patients later diagnosed with Hashimoto's thyroiditis [18]. Unfortunately, in many instances these cases were misdiagnosed as psychiatric disorders before being correctly diagnosed as due to thyroid hormone deficiency.

Lab. Investigations

In areas with sufficient iodine, an elevated serum thyrotropin concentration is often viewed as evidence of chronic autoimmune thyroiditis, and in studies in these areas, at least half the subjects with serum thyrotropin values higher than 5 mU per liter and 80 percent with values higher than 10 mU per liter have thyroid antibodies.

Autoimmune thyroid disease is detected most easily by measuring circulating antibody against thyroid peroxidase (TPO) and Thyroglobulin (Tg) [19]. Thyroid peroxidase (TPO) is a key enzyme in the synthesis of thyroid hormone and is a major antigen corresponding to thyroid anti-microsomal autoantibodies [20]. Highly sensitive assays of TPOAb using radioimmunoassays and enzyme immunoassays have been developed following a hemagglutination assay technique [21].

Guntekunst, et al. [22] found detectable AMA in 87% of cases while Poropatich, et al. [23] found AMA positive in 25/48 i.e. 52% cases.

Serum thyroid microsomal antibody levels were positive in 62.5% cases in the study by Jayram, et al. [24] while 65.1% cases showed positive titres in the study by Bhatia, et al. [9].

Singh, et al. [25] reported AMA positivity in 79.3% and anti-thyroglobulin positivity in 67.3%. 11.3% of their cases were negative for both antibodies.

Backer B A, et al., in 1981 [26], suggested that anti-thyroglobulin antibody determination offers no particular advantage over anti-microsomal antibody titres. 61 / 65 patients in their study showed positive AMA levels while only 15/65 patients had positive anti-thyroglobulin levels. In subjects with a clinical diagnosis of Hashimoto's thyroiditis and negative antibody results, fine-needle aspiration biopsy remains useful in establishing the diagnosis.

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 [4, 26].

Materials and methods

This was a retrospective study carried out in Department of Pathology, KEM Hospital, Mumbai, Maharashtra.

All cases diagnosed as chronic lymphocytic thyroiditis and mixed thyroiditis in a two year period from January 2010 to December 2011 formed the study group.

The terminology autoimmune or Hashimoto's thyroiditis was not used while giving the cytologic diagnosis, as is the prevalent practice in our institute. 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. This category represents autoimmune thyroiditis in our study.

The clinical history, TFT 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.

TFTs obtained by chemiluminescent technique. Reference range of TFTs was as per **Table - 1**.

Table – 1: Reference range of thyroid function test [28].

Parameters	Reference range
T_3	60-160µg/dL
T_4	5-12.5µg/dL
TSH	0.5-5.0mIU/L

Results

In 2 year period, i.e. from January 2010 to December 2011, 7,756 FNACs were performed and of these 1113 were thyroid FNACs (**Table – 2**).

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

	Number	Percentage
Total FNACs	7756	100
Thyroid FNACs	1113	14.4

Thyroid aspirations accounted for 14.4% of all FNAs. 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.

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 – 3**).

Table – 3: Cases of autoimmune thyroiditis (n=150 cases).

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

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 the age group of 21-40 years, maximum number of cases being 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 – 4**).

Table - 4: 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

110 /150 i.e.73.3% patients were euthyroid while 32 (21.3%) patients were hypothyroid at the time of FNAC (**Table – 5**). 2 patients who were euthyroid at the time of FNA became hypothyroid on follow up. Only 5.3% patients showed evidence of hyperthyroidism. T3 and T4 levels were normal in 121 and 130 cases respectively while they were decreased in 20 and 14 cases respectively. 12 patients showed evidence of subclinical hypothyroidism (Increased TSH with normal T3, T4).

Table - 5: Thyroid hormone status (n = 150).

Thyroid status	TSH	Number
Euthyroid	Normal	110
Hypothyroid	Increased	32
Hyperthyroid	Decreased	08

All the 8 cases with a hyperthyroid status were symptomatic, while in the euthyroid and hypothyroid patients only 46% and 53% patients respectively were symptomatic (**Table – 6**).

AMA titre was not available in 53 cases. 85.6% cases with AMA titre available showed AMA positivity (**Table – 7**).

81.9% of the euthyroid patients, 95.4% of the hypothyroid patients and 100% of the hyperthyroid patients showed AMA positivity (**Table – 8**).

Discussion

Incidence

The overall incidence of thyroiditis in our study was 13.6% while that of autoimmune thyroiditis was 13.4%.

The incidence of autoimmune thyroiditis in literature has been quite variable, the prevalence in general population varies from 0.3 to 5% [29, 30]. Studies that estimated the incidence in thyroid aspirates have also showed a wide range from 7.5 to 64%. Three large studies that analysed thyroid aspirates, namely those by Kapila, et al. [31], Gagneten, et al. [32] and Staii, et al. [29], 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

Autoimmune thyroiditis is more common in females and the reported mean age in literature is as high as 58 years in the Whickham survey [33]. Livolsi described the patient population predominantly affected as females over 40 years

with a M:F ratio of 1:20 [16]. 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. [9], carried out in Indian patients, where the peak incidence was also between 21 – 40 years. Kapila, et al. [31] too reported maximum cases in the age group of 16 – 35 years. This disparity between the ages in the Western and Indian literature may be explained by the theory put forth by Kumar, et al. [8] wherein they have proposed that Hashimoto's thyroiditis occurs earlier in Iodine deficient areas such as ours, compared to Iodine sufficient areas.

Table - 6: Correlation of thyroid status with clinical presentation (n=150).

Clinical presentation	Euthyroid	Hypothyroid	Hyperthyroid
Only enlargement of thyroid (Asymptomatic) (n = 74)	59	15	0
Symptomatic with enlargement of thyroid (n = 76)	51	17	08
Total	110	32	08

Table - 7: Anti-microsomal antibody (AMA) titre (n=97).

AMA status	Number	%
AMA Results available	97	100
AMA Positive	83	85.6
AMA Negative	14	14.4

Table - 8: Correlation of thyroid status and AMA titre.

Thyroid status	AMA Positive (n=83)	AMA Negative (n=14)	AMA not available
Euthyroid (n = 110)	59	13	38
Hypothyroid (n = 32)	21	01	10
Hyperthyroid (n = 8)	03	-	05

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. [34] have proposed that chronic lymphocytic thyroiditis must be ruled out in all children presenting with a firm goiter as only 20.5% of their patients had clinical symptoms.

Clinical presentation

74 patients (49%) had no symptoms other than thyroid enlargement while the 76 patients who were symptomatic showed pressure symptoms, menstrual irregularities, heat and cold intolerance, weight gain or loss etc. 29.3% patients in Guntekunst, et al. [22] study were also asymptomatic.

In both groups grade I and grade II enlargement of thyroid (goitre) were common, seen in 72/74 patients of the goitre only group and 69/76 patients of the symptomatic group. 81.8% of the euthyroid patients and 81.2% of the hypothyroid patients had diffused enlargement of thyroid clinically.

Pressure symptoms were more common with grade III/IV thyroid enlargement. Only 8 patients had definite symptoms of hypothyroidism.

Thyroid profile and AMA titre

TSH was elevated in 32 (21.3%) of cases and they showed either decreased (20/32) or normal T3, T4 (12/32).

Normal T3, T4 levels in the presence of elevated TSH indicates sub clinical hypothyroidism (SCH). The incidence of SCH in our study was 8% which compared well to the available literature on Indian population where subclinical

hypothyroidism is reported in 8–17% patients [5].

Prevalence of euthyroid autoimmune thyroiditis appeared high in our study, 73.3% of the patients were euthyroid [29]. 81.9% of these patients had elevated anti-microsomal antibodies. This data suggests that positive serum anti-thyroid antibodies in subjects without overt thyroid disease may indicate the existence of lymphocytic infiltration in the thyroid gland, as was confirmed by FNAC in these cases, and these cases may represent subclinical autoimmune thyroiditis [35].

AMA titre was available in 97 cases. 85.6% cases with AMA titre available showed AMA positivity. 81.9% of the euthyroid patients, 95.4% of the hypothyroid patients and 100% of the hyperthyroid patients showed AMA positivity.

Guntekunst, et al. [22] found detectable AMA in 87% of cases. Serum thyroid microsomal antibody levels were positive in 62.5% cases in the study by Jayram, et al. [24] while 65.1% cases showed positive titres in the study by Bhatia, et al. [9]; Singh, et al. [25] reported AMA positivity in 79.3% and anti-thyroglobulin positivity in 67.3%. 11.3% of their cases were negative for both antibodies. Thus in subjects with a clinical diagnosis of Hashimoto's thyroiditis and negative antibody results, fine-needle aspiration biopsy remains useful in establishing the diagnosis.

Conclusion

Autoimmune thyroiditis was seen more commonly in females, majority cases were seen in age group of 21-40 years. Euthyroid autoimmune thyroiditis was common in our study. Anti-microsomal antibody titre (AMA) was available in 97 cases, out of which 83 were positive i.e.85.6% positivity. Of the cytologically diagnosed cases of autoimmune thyroiditis, 14.4% cases showed AMA negativity. Thus FNAC remains the gold standard for the diagnosis in subjects with a clinical diagnosis of Hashimoto's thyroiditis and negative antibody results.

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