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Cyto-Histologic Correlation in Hashimoto's/ Lymphocytic Thyroiditis With Emphasis on Genetics of Autoimmune Thyroiditis

Ashish Gupta[1], Swati Sharma[2], Mary Mathew[3], Kanthilatha Pai[4], Shankar M Bakkannavar[5]

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Abstract

Introduction: Hashimoto's/Lymphocytic thyroiditis is a common autoimmune disorder which has female preponderance. Autoimmune thyroiditis is considered as a complex interaction and interplay between various genetic and non-genetic factors. Molecular basis of Hashimoto's thyroiditis is not known. Fine needle aspiration cytology being first line of investigation for thyroid lesions is helpful in diagnosing these lesions as well. However, few potential pitfalls in cytology may lead to cytohistologic discordance. *Materials and methods:* This is a retrospective study of one year where all histologic proven cases of Hashimoto's/ Lymphocytic thyroiditis with their corresponding fine needle aspiration cytology slides from pathology database were studied. All FNACs were analyzed in depth and reviewed for cytohistologic correlation. The reasons of cytohistologic discrepancies and discordant cases were analyzed. The genetics of autoimmune thyroiditis was also reviewed from literature. *Results:* Out of total 38 cases of HT/LT analyzed in this study, 89% were females and 11% were males. Mean and median age was found to be 44.4 years and 44 years respectively. Correlation of cytology and histology showed that 50% FNACs' correlated with their respective histologic diagnosis. Major causes of the discrepancies and discordance are reporting on suboptimal smears, cystic fluid samples, and giving over emphasis on a single cytologic feature in rare cell clusters. *Conclusion:* Autoimmune thyroiditis is frequently encountered lesion. Fine needle aspiration cytology is useful in deciding the management of thyroid lesions. In order to restrict the discrepancies and cytodiagnostic errors, one must adhere to the adequacy criterion along with primary fixation, quality of the smear and cellularity. Cytopathologists should be aware of the possible pitfalls and differentiating clues when overlapping features between different lesions are encountered. Also an integrated multidisciplinary approach can be used to minimize potential pitfalls. Many a time the condition can be diagnosed after death as seen in case of few sudden deaths. The unexpectedly brought in thyroid dysfunction is expected in such cases. So the forensic pathologist must keep this entity in mind while dealing with cases of sudden death.

Keywords: Autoimmune; Cyto-histologic discordance; Fine needle aspiration cytology; Genetics; Hashimoto's thyroiditis

Authors Affiliation: [1]Assistant Professor, Department of Pediatrics, Melaka Manipal Medical College, Manipal Campus, Manipal Academy of Higher Education, Manipal, Karnataka 576104, India. [2]Associate Professor, [3]Professor, [4]Professor and Head, Department of Pathology, [5]Associate Professor, Department of Forensic Medicine, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka 576104, India.

Corresponding Author: Swati Sharma, Associate Professor, Dept of Pathology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka 576104, India.

E-mail: swatisharma79@yahoo.com

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Introduction

Hashimoto's/Lymphocytic thyroiditis (HT/LT) is one of the most common autoimmune disorders. Hashimoto's thyroiditis (HT) has a prevalence rate of 1–4% and reported incidence of 30–60/100000 population per year.[1] This disease is more common in females. Its occurrence may be stimulated in genetically susceptible individuals by a number of factors including female gender, immunological changes occurring in postpartum period, fetal microchimerism, amount of iodine intake by

the individual and other environmental agents. At genetic level, few susceptibility genes have been identified probable causing development and progression of this disease process. Some of these genes are specific for this autoimmune process in thyroid gland while few others are found to be common for various other autoimmune disorders.[2]

Fine needle aspiration cytology (FNAC) is an easy, cost-effective and useful investigation for thyroid lesions. It has become a standard first line of investigation for evaluation of thyroid nodules. Since FNAC gives initial results about the nature of the lesion, it helps in determining if an invasive procedure is required for the patient. Thus, helping to avoid unnecessary surgeries for benign diseases. Although FNAC of thyroid nodules has shown high sensitivity and specificity for detecting neoplasms, still many diagnostic difficulties and limitations exist leading to false-positive and false-negative results. HT/LT is considered as one particular cause of both false-positive and false-negative results[3-5], however, in few studies, FNAC sensitivity for this lesion has been reported up to 92%.[6] Thyroiditis is usually missed or misinterpreted in cytological smears showing cytological evidence of hyperplasia as in Graves' disease or abundant colloid. Also follicular cells that exhibit some features of papillary carcinoma and a minimum lymphoid population in the background can cause a diagnostic pitfall. Marked hürthle cell change with sparse inflammatory cells mimicking Hürthle cell neoplasm can also lead to misinterpretation.[6,7]

Aims and Objectives

The aims and objectives of this one-year retrospective study were.

1. To analyze and correlate the cytological findings with respective histological features in HT/LT cases identified for this study.
2. To study the discordant cases in detail and to evaluate the possible causes of these discrepancies in cytology and histopathology.
3. To study the clinical parameters and review the genetic aspect of autoimmune thyroiditis.
4. To review Medicolegal implications of autoimmune thyroiditis.

Materials and Methods

This is one year retrospective study. As a protocol, permission from institutional ethics committee was taken prior to the commencement of this study (IEC-14.391). A total of 76 cases of HT/LT in one year were retrieved from histopathology database. Corresponding FNACs were available for 38 cases. Inclusion criteria was all histopathological proven cases of HT/LT where prior FNAC has been performed and cytological diagnosis was made. Exclusion criteria included the HT/LT cases where prior cytology has not been done, cytology slides (PAP/MGG stained) and/or paraffin embedded slides/blocks for histopathology studies were not available. Cases with other associated lesions (benign/malignant) were also excluded. The only clinical parameters considered were patient's age and gender which was available from the pathology requisition forms and reports. All the cytology slides, histology slides and blocks and clinical details were studied. All FNACs were analyzed in depth and reviewed for cytohistologic correlation. The reasons of cytohistologic discrepancies and discordant cases were discussed.

Results

Out of total 38 cases of HT/LT analyzed in this study, 89% were females and 11% were males. Mean and median age was found to be 44.4 years and 44 years respectively. All the cases were reviewed for histopathology findings and diagnosis of HT/ LT was confirmed. None of the cases had any coexisting or associated benign or malignant lesions. The results of cytological findings were analyzed and given in the Table 1.

Table 1: Cytology reports of the cases

Cytology report	No of cases (*n*)
Hashimoto's/Lymphocytic thyroiditis	19
Papillary carcinoma thyroid	2
Follicular neoplasm	3
Colloid nodule with cystic change	10
Inconclusive/Inadequate	4

On reviewing of cytology slides it was found, that out of 10 cases of colloid nodule with cystic changes, 5 were suboptimal smears.Correlation of cytology and histology showed that 19(50%) FNACs' correlated with their respective histologic diagnosis. The discrepancies and discordance occurring, was found to be due to following causes as mentioned in Table 2.

Table 2: Causes of Cytohistologic discrepancies

Discrepancy	No of cases	Percentage
FNA sampling error (Inadequate)	4/38	10.5
Suboptimal smears	5/38	13.2
Cyto-diagnostic error	10/38	26.3
Papillary carcinoma	2	
Follicular neoplasm	3	
Colloid goiter with cystic change	5	

Among the cytodiagnostic errors, major discordance causing significant effect on patient care was seen in 5/38 (13.2%) cases, where 2 and 3 cases were given malignant diagnosis of papillary carcinoma and follicular neoplasm of thyroid respectively. Rest 5 cases were given benign cytologic diagnosis, which did not correlate with histology subsequently. We have not calculated the false positive and false negative cases in our study as we have not included the cases with cytologic diagnosis of HT/LT with a subsequent different histologic diagnosis.

Discussion

HT was originally described by Hakaru Hashimoto in the year 1912.[8] This is the most prevalent autoimmune thyroid disorder. Patients usually present with a diffuse or less frequently nodular non-tender enlargement of the thyroid gland. Biochemistry reveals hypothyroidism, and the presence of thyroglobulin and peroxidase antibodies in the serum of the individual.[9] At times, patients may not develop thyroid swelling but possess characteristic autoantibodies in the serum.[2]

The etio-pathogenesis for autoimmune thyroiditis is yet to be established completely. Few factors known to play a significant role in its development include genetic susceptibility for the disease. The mechanisms underlying the genetic predisposition are unknown. This has been confirmed predominantly by familial and twin studies. Although a hereditary component in the pathogenesis has been recognized, the inheritance process is complex, involving multiple genes with variable penetrances. Moreover, many loci have been identified, the candidate genes had still not been found. Single-nucleotide polymorphism (SNP) of the thyroglobulin gene (TG; OMIM*188450) and Zinc finger gene in autoimmune thyroid disease 1 (ZFAT1; OMIM*610931) has been found to be associated with susceptibility to autoimmune thyroid disease (OMIM #608175) showing linkage to 8q24 region. Several studies have shown the genes which are associated with the occurrence, progression and severity of autoimmune thyroiditis. The implicated genes include genes for human leukocyte antigen (HLA), cytotoxic T lymphocyte antigen-4, protein tyrosine phosphatase nonreceptor-type 22, thyroglobulin, vitamin D receptor, cytokines and many more. Other endogenous factors for the development of autoimmunity are female gender, pregnancy and postpartum period and fetal microchimerism. Exogenous environmental factors which influence HT development include amount of iodine intake, ingestion of certain drugs, associated infections and exposure to different chemicals. It is believed that disturbed self-tolerance accompanied by the increased antigen presentation is a prerequisite whereas interaction of thyroid cells, antigen presenting cells, and T cells are required for the development of thyroid autoimmunity. The cytokines secreted in this process lead to predominantly T-helper type 1 (Th1) as well as Th 17 response. At the end, thyroid destruction occurs due to the apoptotic processes and T-cell mediated cytotoxicity.[2,10] Molecular basis of HT is not known yet.

The overall incidence of HT is known to be increasing in the recent times and has become nearly 10 times more common in this century when compared to early 1990s. This increase is probably due to excess iodine intake, particularly in the coastal areas.[11,12] The abundance of female cases in our series (89%) was consistent with other studies.[13,14]

A diagnosis of HT/LT is often clinical based on presence of serum auto antibodies.[15] Still, ultrasound neck is done to look for the presence of dominant nodules. FNAC is performed if there is a dominant noduleor when there is a recent increase in the size of the swelling.[16] Cytologic features for HT/LT are oxyphilic (Hürthle) cells, infiltration of follicles by lymphoid cells, plasma cells and the presence of moderate amount of colloid in the background. The histologic findings include a diffuse lymphoid infiltration in the thyroid parenchyma, scattered plasma cells or histiocytes, atrophy of follicular cells and oncocytic changes of follicular cells called as Hürthle or Askanazy cells. Eventually, as the disease progresses, destruction of thyroid parenchyma with fibrous replacement occurs.[8,9,17] While giving a diagnosis of HT/LT, a dilemma and difficulty may result from coexistence of a benign or a malignant tumor or changes that occur in epithelial cell morphology in HT/LT mimicking thyroid neoplasms.[15,16,18] The precise and early diagnosis of HT/LT is of paramount importance as patients subsequently develop hypothyroidism and require lifelong supplementation of thyroxin. These

cases also harbor an increased risk of development of extra-nodal marginal B zone lymphoma. Since the frequency of development of malignancy varies between 0.5–23.5%, long term follow up is recommended.[7] One should not over-diagnose this entity as neoplasms or underdiagnose it as some benign lesion as the management would be varied in different lesions.

FNAC is a primary diagnostic tool for evaluation of thyroid nodules and a precis ecytologic diagnosis obviates unrequired surgeries. The important steps to be followed for any FNAC include careful sample procurement, appropriate sample preparation and accurate interpretation by cytopathologists. This will lead to precise cytologic diagnosis and reduce discrepancies.[19] FNAC is cost-effective first line of investigation in diagnosing HT/LT. However, it has got some pitfalls causing diagnostic dilemma. More importantly, there is an overlap in the morphological features of HT on cytological preparations with other thyroid lesions like multinodular goiter with degenerative changes, follicular neoplasm, hürthle cell neoplasm, papillary carcinoma, reactive lymphnode and lymphoma.[20]

Nearly 23.7% of the cases in the present study were either inadequate or suboptimal for opinion on cytology, hence could not be reported. Our result is little higher than others as reported in literature. Previous studies have shown around 10–20% of aspirates as unsatisfactory.[21,22] These include inadequate number of thyroid follicular cells, cystic fluid, bloody smears, poor technique in obtaining the sample or impropercytologic preparation. The Papanicolaou Society of Cytopathology task force on Standards of Practice recommends that "aspirators who persistently produce a high rate of unsatisfactory aspirates (>15%) should be identified and given remedial training".[23] However, in our study, FNAC samples were taken by different operators with varying skill levels and experience. Also poor cellularity of the aspirated samples in cystic lesions and suboptimal preparations can often be misinterpreted as benign lesions, which has also been observed in 5 cases in our study. In this regard, one should remember that cystic change in thyroid lesions is a common diagnostic pitfall and precise diagnosis cannot be offered if sample is taken from cystic areas. Aspiration from multiple sites and from solid areas is useful in preventing sampling error. Ultrasound-guided FNAC of cystic thyroid nodule is recommended for better yield of cells. Finally, strict criteria for specimen adequacy must be followed to reduce the erroneous diagnosis and improve the overall accuracy.[19]

The false negative rate (FNR) is defined as the percentage of patients given benign diagnosis on cytology, where malignancy was later confirmed on histopathology. Literature reports FNR ranging from 1.5–11.5%.[24–26] It is seen that FNR is higher if cases with negative cytological diagnosis were followed up for months or years.[7,24] In our study this parameter was not calculated as we have selected a cohort of cases with known histologic diagnosis of HT/LT where prior FNAC was done.

The false positive rate (FPR) is defined as the percentage of patients with malignant FNAC result but found to have benign lesion on histology. Various authors have reported FPR ranging from 0 to 8% in their studies.[24,27] In one study, two cases were reported as malignant but later on diagnosed to be Hashimoto's thyroiditis and nodular colloid goiter with focal areas of adenomatous hyperplasia.[24] In our study, 5 cases were diagnosed as malignant on cytology but on histologic examination subsequently, were HT/LT. The cytologic challenge in identifying a thyroid neoplasm associated with HT/LT is well established. Many studies done in the past have pointed out the importance of identifying thyroid neoplasm that may be disguised by a background of lymphoid cells of HT/LT on FNAC preparations. Many specific cytologic criteria have also been suggested to differentiate between thyroid neoplasm and changes occurring due to HT/LT.[18,28,29] Potential pitfalls causing false positivity for malignancy in HT/LT cases are cytologic atypia occurring in autoimmune thyroiditis, amount of background inflammation, sparse cell yield, coexisting thyrotoxicity and neoplasms. Features suggesting a possibility of malignancy include dyscohesive cell clusters, epithelial preponderance over inflammation, nuclear crowding and atypia.[20] Cytologic features which may lead to overdiagnosis of papillary carcinoma of thyroid are powdery nuclear chromatin, presence of nuclear grooves or inclusions and paucity of background lymphocytes. One very important clue which may be helpful in differentiating HT/LT from thyroid neoplasms is lymphocytes infiltrating follicular groups. In this regard, papillary carcinomas display characteristic malignant features in multiple cell clusters and these clusters do not possess infiltrating lymphocytes or may rarely have lymphocytes only at their periphery. In our study, the two cases which were false positive for papillary carcinoma thyroid, on review had focal suspicious nuclear features and scant colloid. True lymphocytic infiltration of the follicular cell clusters were present. However, the frozen section for both cases

did not reveal malignancy and hence unnecessary surgeries could be prevented. We found 3 cases of false positive follicular neoplasm in this study. A microfollicular pattern with paucity of background lymphocytes has been considered as the major pitfall in overdiagnosing follicular neoplasm.[3] Again, in this regard, the presence of lymphocytes closely infiltrating follicular groups serve as an important diagnostic clue.It is important to remember that the number of lymphocytes in FNA alone is not a feature that can distinguish HT/LT from a thyroid neoplasm.[18,30] In our study, presence of sparse lymphoid cells along with microfollicular pattern was the predominant reason for this overdiagnosis. It is suggested that even with predominant microfollicular pattern, it is preferable to render a diagnosis of suspicious for follicular neoplasm. And in presence of scattered lymphocytes, even if sparse, search for other features of HT/LT is recommended. The degree of nuclear pleomorphism of the follicular cells is not considered to be an useful feature to differentiate between the two lesions.[3]

Literature review documents many studies stating difficulty in differentiating between HT/LT from Hürthle cell neoplasm on cytology, leading to cytohistologic discordance.[4] The reason for this dilemma is the proportion of Hürthle cells and lymphoid cells. Hürthle cell metaplasia with nodule formation is a known phenomenon and can be seen as a histologic feature in HT/LT. This must not be overlooked while reporting Hürthle cell rich cytological smears. Cytological features which favor thyroiditis over neoplasm in a smear rich with Hürthle cells are absence of poorly organized cell clusters having nuclear pleomorphism, particularly anisonucleosis of Hürthle cells.[4,13,15,19] Another area of potential pitfall is lymphoid cell rich smears, where cytologic examination reveals dense population of lymphoid cells with occasional epithelial cells. Cytologic diagnosis of HT/LT and lymphoma is difficult and a diagnostic challenge because of the presence of heterogenous population of lymphoid cells in both. The differences in these lesions are very subtle, however, presence of polymorphous population of lymphoid cells, predominantly small mature lymphocytes admixed with plasma cells and presence of germinal center cells favor HT/LT.[19,31,32]

In this study, it is noted that most errors occur when too much emphasis is given on a single cytologic feature. We must not overemphasize classic neoplastic features on rare cell clusters. This may cause overdiagnosis and finally result in cytohistologic discrepancy. Multiple aspirations from different parts of the lesion are required to give a clear picture of cytologic features, reduce over interpretation and help in rendering precise diagnosis.[19,30] One should be careful while giving a positive diagnosis on cytology smears with only a few cell clusters of suspicion. It is recommended to inform the clinician about the limitations of FNAC in these diagnostically challenging cases.[3,19]

If such cases are missed during the lifetime or inaccurately diagnosed because of limitations of FNAC and the clinician overlooks into them, the condition could be a reason of fatality in future. There are cases reported in literature regarding sudden unexpected deaths due to Hashimoto's thyroiditis.[33] Such cases are diagnosed only after the postmortem examination. We should keep in mind the various causes of death associate with Hashimoto's thyroiditis like autoimmune myocarditis,[34] undiagnosed spontaneous intracranial hypotension,[35] etc.

Conclusion

HT/LT is commonly encountered thyroid lesion in day-to-day practice. Presently, autoimmune thyroiditis is considered as a complex interaction and interplay between various genetic and non-genetic factors leading to enhancement in antigen presentation and changes in the immune tolerance of the individual, thus developing autoimmunity. This mechanism is the cause for the development of various clinical features which finally lead to the destruction of the thyroid gland. Molecular basis of HT is not known.

FNAC is an easy, economic, safe, sensitive and specific procedure for the initial evaluation of thyroid nodules. In majority of the cases, correct cytologic diagnosis can be rendered, hence, useful in deciding the further management of the patient. In order to restrict the discrepancies and cyto-diagnostic errors, it is recommended to strictly adhere to the FNAC adequacy criterion. Adequacy should take into account components like primary fixation, quality of the smear and cellularity. Offering a definite diagnosis on suboptimal FNA samples is a very significant and avoidable source of cytohistologic discordance. Since cystic change in the thyroid lesions is a common cause of diagnostic pitfall, aspirations from multiple sites, preferably from the solid areas are recommended. Also sincere and meticulous examination by cyto-pathologist aids in reducing the number of discrepant cases and erroneous diagnosis. Pathologists should be aware of these possible pitfalls and differentiating clues when

overlapping features are seen in cytology. This will help in reducing the number of cyto-histologic discordance rates. However, in certain difficult situations an integrated multidisciplinary approach may minimize potential pitfalls.

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