

Commentary

Spectrum of Hashimoto's thyroiditis: Clinical, biochemical & cytomorphologic profile

Hashimoto's thyroiditis (HT), first described in 1912 by Hakaru Hashimoto, is the most common autoimmune thyroid disease and the commonest cause of hypothyroidism¹. With 5-10 times predominance over men, reported prevalence in women is 1-2 per cent². HT or chronic lymphocytic or autoimmune thyroiditis is characterized by infiltration of lymphocytes and formation of Askanazy (Hürthle) cells. HT typically presents with hypothyroidism, painless enlargement of thyroid gland (goiter), or both; 90 per cent of HT patients have high anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibody. Cytomorphological diagnosis may be superior in children and initial stages of HT as antibody production may be confined to intrathyroidal lymphocytes or localized areas of HT³. Staii *et al*⁴ reported high prevalence (13.4%) of HT diagnosed by ultrasound-guided FNA (fine needle aspiration) analysis with 7.4 per cent euthyroid and 6 per cent clinically hypothyroid⁴. There was a lack of cytological correlation with TPO autoantibody positivity⁴. The hallmark of diagnosis of HT is the presence of TPO autoantibodies. Yet, only about half of the patients tested positive for anti-TPO in the euthyroid subgroup of HT⁴. Cytological diagnosis of HT may precede clinical diagnosis, inspite of the fact that in most organ specific autoimmune diseases humoral immunity heralds tissue infiltrative damage. Given the wide range of normal values for thyroid stimulating hormone (TSH) and the variability of presence of TPO autoantibodies in HT, it is conceivable that early Hashimoto's autoimmune process might be clinically missed. Moreover, subclinical and clinical hypothyroidism is associated with cardiovascular and neuropsychiatric morbidities, thus finding high prevalence of HT on cytology, especially in euthyroid patients is clinically significant. Most of HT patients are pre-menopausal women and the risk of poor obstetrical and foetal outcome is increased with even relatively mild or subclinical thyroxine deficiency.

Diagnosis of HT is made clinically and biochemically and supported by high TPO and anti Tg antibody, biopsy is not indicated in most. However, subclinical HT with raised antibodies and normal T4 (with normal or mildly raised TSH) is being diagnosed frequently because of widespread use of thyroid function tests. Little is known about progression of euthyroid to hypothyroid state in HT. At least in children progression from euthyroid to hypothyroid in HT has been suggested⁵. Also there is evidence relating to progression of subclinical to overt hypothyroidism in adults with HT⁶.

Sonographic findings of HT include diffuse goiter with decreased echogenicity, heterogeneity, hypervascularity, and presence of hypoechoic micronodules with echogenic rim⁷. However, some studies have found decreased Doppler blood flow in Hashimoto's thyroiditis as differentiating feature from Grave's disease⁸.

Countrywide salt iodization, to prevent major functional consequences of endemic goiter and nutritional iodine deficiency, has been achieved in India with more than 70 per cent of the population consuming iodized salt⁹. In the post-iodization phase, 23 per cent prevalence of goiter in 14,762 children from all over India was reported¹⁰. The authors suggested that despite iodization, the prevalence of goiter has not dramatically declined. A significantly higher level of median urinary thiocyanate (USCN) excretion was noted in goitrous subjects (0.75 mg/dl) when compared with controls (0.64 mg/dl; $P < 0.001$). It was noted that thyroid autoimmunity could only partly explain the goiter. Thus, the role of goitrogens needs further exploration. In a landmark study in 6283 schoolgirls in India, 7.5 per cent had evidence of autoimmune thyroiditis on FNAC with subclinical and overt hypothyroidism in 15 and 6.5 per cent, respectively¹¹. A population-based Indian study

found that about 12 per cent of adults had a palpable goiter with 3.9 and 9.4 per cent prevalence of clinical and subclinical hypothyroidism, respectively, while 53 per cent of subclinical hypothyroidism had positive anti-TPO antibodies¹². Prevalence of autoantibody positivity in iodine deficient areas rises after initiating iodine supplementation. Iodine can cause autoimmune thyroiditis, by generating reactive oxygen intermediates, increase in Tg immunogenicity and directly stimulate the immune system particularly dendritic cells and a 3-fold increase in lymphocytic infiltration of thyroid. Iodine-induced thyroid autoimmunity is related to Tg antibody and the unmasking of a cryptic epitope on Tg contributes to this relationship in humans¹³.

HT commonly presents with firm and painless goiter. Goiter in HT is variable in size, rarely painful and is often lobulated making it difficult to distinguish from multinodular goiter. Presence of pain, rapidly enlarging neck mass and enhanced posterior echoes on ultrasonography in HT may indicate primary thyroid B-cell lymphoma¹⁴. Presumably prolonged stimulation of intrathyroidal B cells results in emergence of malignant clone. Fine needle aspiration biopsy (FNAB) with immunophenotypic analysis may be needed if there is pain, dominant nodule or rapid enlargement of goiter. The link between HT and papillary thyroid cancer (PTC) is controversial. The linkage between these two disorders is appealing because the concept of chronic inflammation leading to a neoplastic condition is well established for other tissues. Moreover, higher TSH level in patients with thyroid nodules has been found to be associated with risk of differentiated thyroid cancer so active remodelling of thyroid epithelium in cytological HT may explain in part the increased risk for differentiated thyroid cancer observed in patients with elevated but within normal TSH⁴. Some studies propose a genetic link between HT and PTC involving the PI3K/Akt pathway and RET/PTC gene rearrangement. A recent meta-analysis has found that population-based FNAB studies of PTC in HT report no linkage (RR: 0.69), whereas studies of thyroidectomy specimens report a positive relationship (RR: 1.59) probably due to selection bias¹⁵. It is also suggested that HT appears to confer a better prognosis in patients with PTC¹⁵. At present, there is no valid established criterion to identify those patients with HT at a higher risk of developing PTC. Careful observation and follow up of HT patients is recommended, especially those with nodular variants¹⁵. More prospective studies with longer follow up are needed to further elucidate this complex relationship.

In this issue, Thomas *et al*¹⁶ studied the clinical, biochemical, antibody levels, ultrasound and cytomorphologic characteristics of 144 patients with cytological diagnosis of HT in an endemic zone for goiter, with widespread use of iodized salt. They found that 90 per cent of HT patients were females mainly between 21-40 yr of age similar to other Indian studies¹⁷. In western literature HT occurs seven times more in women with peak incidence between 40-60 years¹⁸. In this study 90 per cent of HT patients had symmetrical, firm, diffuse painless goiter. Thomas *et al*¹⁶ reported that goiter was the commonest presenting complaint with majority (61%) having diffuse goiter. Most (46%) were hypothyroid (subclinical and overt), 33 per cent patients were euthyroid and 21 per cent were hyperthyroid on evaluation. Among the hypothyroid patients, only 38 per cent showed overt hypothyroidism similar to previous studies in India¹⁷. Hashimoto's disease may coexist with Graves' disease. Thomas *et al*¹⁶ found that 93 per cent of the study subjects with HT were anti TPO positive and 92 per cent were antithyroglobulin antibodies (anti Tg) positive. Pearce *et al*¹⁹ found TPO antibodies in 90-95 per cent of HT but anti-Tg antibodies in only 20-50 per cent. TSH receptor blocking antibodies may cause transient hypothyroidism in infants born to mothers with Hashimoto's disease²⁰. Ultrasonography in the current study showed heterogeneous echotexture with increased vascularity. The authors reported three cases of papillary carcinoma and one of medullary carcinoma associated with HT on cytology. Papillary carcinoma thyroid and primary thyroid lymphoma are commonly associated neoplasms with HT. Primary thyroid lymphoma is 60 to 80 times more common in patients with HT than in the general population²¹. HT is associated, although less strongly, with papillary carcinoma. Thomas *et al*¹⁶ suggested that in an endemic zone for goiter, all women of the child bearing age should be screened for HT.

The importance of iodine deficiency and endemic goiter, thyroid autonomy, non-autoimmune nodular hyperthyroidism and congenital hypothyroidism cannot be underestimated in the Indian context. Iodine intake strongly affects the spectrum of thyroid diseases, but the long term benefits of correcting iodine deficiency (decreased prevalence of goiter and congenital hypothyroidism in younger subjects and reduced frequency of non-autoimmune autonomous hyperthyroidism in older subjects) far outweigh the risk of development of thyroid autoimmunity and mild hypothyroidism in youngsters²². In the post-iodization

era HT is probably the commonest cause of goiter and hypothyroidism especially in women of child bearing age, but the contributory effect of goitrogens needs clarification. Euthyroid stage of HT exists which may progress to overt hypothyroidism especially in young. Goiter or clinical hypothyroidism are indications for treatment of HT. Future research should focus on early diagnosis of HT, which is still evolving and further exploration is required. We need to detect HT early to prevent the deleterious effect of unrecognized hypothyroidism especially in children and pregnant woman, where treatment of even a mildly elevated TSH improves neuropsychological developmental and foetal outcomes. Molecular association and pathogenesis of HT and primary thyroid lymphoma needs in-depth research. Mechanistic association of HT with PTC is controversial but prospective long term follow up studies of patients with HT, without selection bias will help to unravel the mystery.

Debmalya Sanyal

Department of Endocrinology

KPC Medical College

Kolkata 700 032, West Bengal, India

drdebmalysanyal@gmail.com

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