Diagnostic Approach to Thyroid Nodules.

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ABSTRACT

Derangement of thyroid function is a common clinical problem, with variable clinical presentations ranging from subtle, incidentally discovered disorders to overt disease, with frank disturbances of hormone levels and visible thyroid enlargement. In addition, there are the autoimmune thyroid disorders, and the neoplastic enlargements which result in palpable nodules. A large amount of new information has become available in recent times. They provide a comprehensive approach to diagnosis of thyroid nodules, ranging from initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, and their management. Recommendations regarding the initial management of thyroid cancer include those relating to optimal surgical management, radioiodine remnant ablation, and suppression therapy using levothyroxine. Recommendations related to long-term management of differentiated thyroid cancer include those related to surveillance for recurrent disease using ultrasound and serum thyroglobulin as well as those related to management of recurrent and metastatic disease. We went through the published literature available electronically and assessed the various studies and their results. The results were reviewed carefully and interpreted in order to analyse the approach to diagnosis of thyroid swellings, especially in the Indian context. Although a detailed review is outside the scope of this paper, we will attempt to discuss some of these guidelines, especially in light of the scenario in our region.

Keywords: Thyroid nodule, management, FNAC, Clinical guidelines.

INTRODUCTION

Derangement of thyroid function is a common clinical problem, with variable clinical presentations ranging from subtle, incidentally discovered disorders to overt disease, with frank disturbances of hormone levels and visible thyroid enlargement. The clinical presentation may vary from a hypofunctional thyroid (hypothyroidism) to over secretion of thyroid hormones. In addition, there are the autoimmune thyroid disorders, and the neoplastic enlargements which result in palpable nodules. A discrete thyroid nodule maybe the initial presentation in both benign as well as malignant neoplasms. The prevalence of clinically inapparent thyroid nodules (on ultrasonography, USG) ranges from 20% to 76% in the general population.¹ Moreover, 20% to 48% of patients with palpable thyroid nodules are found to have additional nodules on USG.² In India, the incidence of clinically palpable nodules in adults is around 12.2%.³

A large amount of new information has become available in recent times. They provide a comprehensive approach to diagnosis of thyroid nodules, ranging from initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, and their management. The American Association of Clinical Endocrinologists (AACE) have provided a well defined system of approach to thyroid nodules. These cover recommendations related to the initial diagnosis, categorization and management. We went through the published literature available electronically and assessed the various studies and their results. The results were reviewed carefully and interpreted in order to analyse the approach to diagnosis of thyroid swellings, especially in the Indian context. Although a detailed review is outside the scope of this paper, we will attempt to discuss some of these guidelines, especially in light of the scenario in our region.

MAGNITUDE OF THE PROBLEM

The estimated prevalence of thyroid disease in the Indian population is variable. The most common presentation in india is hypothyroidism. This is
primarily attributable to iodine deficiency. In recent times, autoimmunity has increasingly been recognized as a major cause of thyroid enlargement and hypofunction. Around 16.7% of adults in India have anti-thyroid peroxidase (anti-TPO) antibodies and 12% have anti-thyroglobulin (anti-Tg) antibodies.\[3\] In a study on schoolgirls, it was estimated that colloid goitre was the commonest cause, followed by thyroiditis.\[5\] Another study in Delhi showed the incidence of clinically palpable nodules to be around 1.6% with the figures rising to 4.6% and 5.6% in males and females, respectively, after USG. Subclinical hypothyroidism was frequent and anti-TPO antibody levels were raised in 13.3% of subjects.\[6\]

Thyroid cancer is another major problem, especially in the background of autoimmune thyroiditis which is known to be associated with thyroid neoplasms. The age-adjusted incidence rates are 1 and 1.8 for males and females respectively. Papillary cancer is reported to be the commonest histological type.\[7\] This is again a matter of concern since papillary cancer is linked to autoimmune thyroiditis and hence, early recognition of autoimmune thyroid dysfunction is essential and potentially a preventive measure for cancer. In a study by Ahn D et al, out of 269 patients with papillary thyroid cancer, 21.6% (58/269) had concurrent hashimoto’s thyroiditis.\[8\]

**THYROID DISEASE AND DIABETES**

India is facing an epidemic of diabetes mellitus with an estimate of 62.4 million people with diabetes and 77.2 million people with prediabetes according to Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study.\[9\]

The prevalence of thyroid dysfunction is higher among diabetic patients, especially females with type 1 diabetes mellitus.\[10\] Autoimmune thyroiditis is significantly associated with type 1 diabetes.\[11\] Post-partum thyroiditis is also more common in diabetic females.\[12\] From the point of view of management, the clinician needs to be aware of the effect of altered metabolic rates on glucose levels and lipid profile, as there is evidence of disturbances in glycemic control and increased risk of cardiovascular events in these patients.\[13\]

Metabolic syndromes are also associated with thyroid disorders, especially in hypothyroidism.\[14\]

Both thyroid disorders and diabetes (individually) predispose to increased risk of cardiovascular events. It is our view that all patients with thyroid dysfunction, especially hypothyroidism, should be monitored for derangements of glucose and lipid levels. In addition, anti TPO antibody testing should be done along with TSH in diabetic patients, especially females, including expectant mothers. A careful regulation of TSH can help in good glycemic and lipid control also.

**Hormonal evaluation**

The AACE guidelines recommend that the initial step should be estimation of serum Thyroid stimulating hormone (TSH) levels. This is followed by an antibody assay. Anti -TPO (Thyroperoxidase) if TSH levels are high, or free thyroxin and tri-iodothyronine levels if TSH is low. Anti-thyroglobulin (Tg) levels should be assessed only if anti-TPO levels are low and there is clinical indication of chronic lymphocytic thyroiditis. Thyroid receptor antibodies (TrAb) are tested for if TSH levels are low.\[4\]

The 2011 consensus statement by the Endocrine Society of India also\[15\] recommends the estimation of serum TSH, along with USG and aspiration biopsy, for the evaluation of thyroid swellings. Antibody estimation is to be recommended if there is clinical suspicion of autoimmune disease.\[15\]

The general approach is to subject all palpable nodules to aspiration biopsy. Given the high prevalence of subclinical thyroid disorders, especially hypothyroidism and autoimmune disease, we feel that it is prudent to screen all patients with a thyroid nodule for antibodies, apart from imaging and FNAB, as required. This will have two fold benefit - firstly the detection and appropriate treatment of autoimmune thyroid disease, and secondly, screening or followup for malignant change in those patients who have significantly raised antibody levels. However, as we will discuss later, cytological examination should not be relied upon solely. Moreover, the pathologist receives supportive evidence if thyroid function tests are done initially or alongside.

**Ultrasonography**

The AACE recommends the use of USG in all patients at risk of malignancy, and all patients with multinodular goitre or palpable thyroids or suspicious lymphadenopathy. It is not recommended as a screening test in the general population.\[4\]

Certainly, USG has high specificity in diagnosis of thyroid nodules (upto 95% for microcalcifications and upto 91.8% for irregular margins). Findings suspicious of malignancy are a taller-than-wide shape, a spiculated margin, marked hypoechochogenicity and microcalcification. The US findings for benign nodules include isoechochogenicity and a spongiform appearance. USG evaluation can provide excellent insight into the nature of the nodule and the area which is most suited for cytological evaluation. It is also possible to detect other inapparent nodules.\[16\] The recommendations are similar to the consensus statement on USG evaluation by the Endocrine society of India.\[15\]

An important factor to be considered here is that in rural areas of developing countries, there are patients who may not undergo USG evaluation due to financial constraints or lack of access. Therefore, the clinician may have to decide which patient will require this
test, and if needed, this may be done after assessing the pathological report as an initial investigation.

**Aspiration biopsy**

Thyroid FNA has been shown to have good specificity and sensitivity (92 and 83%) respectively in diagnosis of nodular thyroid swellings. The false negative rate varies from 1 to 7% while the incidence of false positive report is up to 7.7%.\[16,17\]

This can be minimized with USG guidance. USG is an excellent modality for selecting specific areas for aspiration.

The 2016 recommendations of AACE regarding the criteria for selection of nodules for FNA are that all nodules larger than 10mm with a high – risk category on USG should undergo cytological evaluation. Nodules 5 - 10mm with suspicious features, nodules in patients with a correlative family history of thyroid cancer, or presence of lymphnodes or extrathyroidal spread should undergo FNA. Nodules which are ‘hot’ on scintigraphy are excluded.\[4\]

The Endocrine society of India consensus statement recommends that all palpable nodules, especially those larger than 1cm in size, should be aspirated. In addition, it is recommended that palpation guided FNA must not be practiced in nonpalpable lesions, lesions with more than 25% cystic areas, nodules with previously inconclusive FNA report and in suspicious nodules.\[15\]

These guidelines are comprehensive and provide a framework within which decisions are to be made, with efficiency and reproducibility. It is necessary to state here that palpation - guided FNA still remains the mainstay of cytological examination in developing regions. It appears that the simple rule to follow would be that all palpable nodules are to be investigated with FNA, especially those with size large than 1cm, or in patients with a relevant clinical history or examination finding.

**Role of Molecular Testing**

FNA cytology accurately diagnoses a benign or malignant lesion in the majority of cases; however, approximately 10-40% of all FNA samples are diagnosed as indeterminate for malignancy, often prompting diagnostic hemithyroidectomy.\[18-22\] This is because cytological features of thyroid lesions with a follicular growth pattern are frequently not sufficiently clear to distinguish between benign and malignant lesions. Currently among surgically removed thyroid nodules only 8 to 56% are found to be malignant.\[23-24\] Such a high volume of unnecessary thyroid surgeries results in additional morbidity and higher health care costs.\[25,26\]

Moreover, patients with malignant tumors and indeterminate FNA cytology typically undergo a limited surgery, i.e. thyroid lobectomy. After the diagnosis of malignancy is established by pathological examination of the removed nodule, these patients require a second operation to complete the thyroidectomy, which is associated with additional costs and morbidity. In addition, 1–3% of nodules diagnosed as benign on FNA cytology are later found to be malignant on follow-up (false-negative FNA), and the delay in treatment places patients at risk for progression of disease during the interval before definitive diagnosis.\[19,24\]

Additional methods to improve the sensitivity and specificity of FNA cytological diagnosis are highly desirable and could have a significant impact on clinical care. Recent advances in molecular genetics of thyroid cancer can be applied to developing new diagnostic markers for FNA samples.\[27,28\] Papillary carcinoma, the most common thyroid malignancy, frequently carries BRAF, RET/PTC, or RAS mutations. These mutually exclusive somatic mutations are found in more than 70% of papillary carcinomas, and some of them are associated with more aggressive tumor behavior.\[29,30-31\] Follicular carcinomas, the second most common type of thyroid cancer, harbor either RAS or PAX8/PPAR mutations, which are identified in approximately 80% of these tumors.\[32\] Several studies have demonstrated the feasibility of detecting BRAF, RET/PTC, or RAS mutations in thyroid FNA samples and have shown that this may improve the cytological FNA diagnosis.\[33-38\]

For both the clinician and the pathologist, the problematic categories are those of nondiagnostic aspirates, those with atypia of undetermined significance and suspicious lesions. In general, these nodules would ideally have to be reaspirated. USG guidance is preferable in such cases.

For example, a very common problem is that only cystic fluid is aspirated without any cells. Such a sample would be considered inadequate and nondiagnostic. However, USG correlation can solve the problem and avoid unnecessary reaspiration. Similarly, atypia can be as a result of artefactual changes, degenerative changes, inflammation, or a feature of a hyperfunctioning thyroid, or secondary to radioablation. So a careful clinical correlation is necessary to avoid misinterpretation. Another potential pitfall is the presence of hypercellular cell groups and scant colloid in a hyperfunctional thyroid. This can lead to a suspicion of neoplasia, especially papillary cancer. Clinical history, thyroid profile or USG findings can solve the problem here and avoid unnecessary reaspiration.

**CONCLUSION**

Based on the review of current literature regarding thyroid disease and diabetes mellitus especially in India, we would like to suggest a few general guidelines.

- Diabetic patients should be screened for thyroid dysfunction at the outset as both hypothyroidism (sub-clinical and overt) and...
metabolic syndromes are recognized risk factors for atherosclerotic cardiovascular disease.

- All patients with a thyroid nodule and hypothyroidism should be evaluated for anti-TPO and not only TSH levels at the start which will help in both detection and treatment of autoimmune thyroid disease, as well as during follow-up for malignant change in those patients who have significantly raised antibody levels.

- In developing regions, palpation guided FNA still remains the mainstay of cytological examination.

- USG should be used in conjunction with FNA where ever possible.

REFERENCES


