Solitary Thyroid Nodule - A Diagnostic Challenge

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Abstract: Most common presentation of thyroid nodule is a lump felt on self examination. They are more common in females; 90% of them are benign in nature, adenoma being the commonest amongst the benign causes. Combined use of fine needle aspiration cytology (FNAC), thyroid scan and ultrasonography (USG) can detect them with 90% accurarcy. An effort has been done here to present a diagnostic approach to a solitary thyroid nodule to evaluate the utility of different investigations in achieving the correct diagnosis.

Introduction

Thyroid nodules are lumps which commonly arise within an otherwise normal thyroid gland. Often these abnormal growths are located at the edge of the thyroid gland, so they can be felt as a lump in the throat. When they are large or are present in thin individuals they can be seen as a lump in the front of the neck. The prevalence of thyroid nodules within a given population depends on a variety of factors that include age, sex, diet, iodine deficiency, and therapeutic and environmental radiation exposure. True solitary nodules occur in 4-7% of the adult population. They are more common in females, and this predisposition exists throughout all age groups. Prevalence increases with age, with spontaneous nodules occurring at a rate of 0.08% per year beginning early in life and extending into the eighth decade. Thyroid nodules are found in 5% of persons at an average age of 60 years.

Most thyroid nodules are benign hyperplastic lesions, but 5-20% of thyroid nodules are true neoplasms. Solitary nodule first seen can be due to asymmetric enlargement of one lobe as in unilateral agenesis, chronic lymphocytic thyroiditis (i.e., Hashimoto thyroiditis), or in simple goiter. In addition, developmental errors, such as ectopic tissue, may cloud the picture. Suspected thyroid nodules merit close attention especially in childhood as the presence of malignancy in such nodules is much more likely than in an adult. This frequency of malignancy is estimated to be 15-25%. In addition, thyroid cancer is much more aggressive in children and is associated with early metastasis to regional lymph nodes and parenchymal organs, most commonly lung and bone.

Major goal in the evaluation of the solitary thyroid nodule is the differentiation of hyperplasia from true neoplasms. Furthermore, the histologic criteria used to distinguish benign from malignant neoplasms can be subtle. Therefore evaluation of solitary thyroid nodules requires the collaboration of the primary care physician, endocrinologist, pathologist, radiologist, and head and neck surgeon to provide comprehensive and appropriate management of this clinical entity. Solitary thyroid nodule may represent a multitude of thyroid disorders, and a thorough knowlwedge of the epidemiology of thyroid disease is of paramount importance. Comprehensive history and physical examination provides the foundation for decision making in management of thyroid nodules. Currently, a variety of serologic and cytogenetic tests, diagnostic imaging studies, and histopathologic techniques exist for the evaluation of a thyroid nodule. Of these methods, fine-needle aspiration biopsy (FNAB) has become the most important tool in the assessment of solitary thyroid nodules.

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Causes

The differential diagnosis of solitary thyroid nodule can be broadly classified into benign and malignant. Generally, most thyroid nodules are **benign** and can be classified as Adenomas, colloid nodules, congenital abnormalities, cysts, infectious nodules, lymphocytic or granulomatous nodules, hyperplastic nodules, thyroditis (Hashimotos and subacute), Radiation to head and neck.

Malignant thyroid nodules can be classified as : (a) *Differentiated:* (1) Papillary adenocarcinoma, (a) Pure papillary adenocarcinoma, (b) Mixed papillary and follicular carcinoma (variants including tall cell, follicular, oxyphyl, solid)

(2) Follicular adenocarcinomas (variants: "malignant adenoma", Hurthle cell carcinoma or oxyphil carcinoma, clear-cell carcinoma, insular carcinoma)

(b) *Medullary carcinoma* - (not a tumor of follicular cells)

(c) *Undifferentiated :* (1) Small cell (to be differentiated from lymphoma), (2) Giant Cell, (3) Carcinosarcoma.

(d) *Miscellaneous :* (1) Lymphoma, sarcoma, (2) Squamous cell epidermoid carcinoma, (3) Fibrosarcoma, (4) Mucoepithelial carcinoma, (5) Metastatic tumor.

Evaluation of Solitary Thyroid Nodule

The evaluation is done by history, examination, metabolic profile, imaging, invasive procedures. Edvaluation should be done keeping three question in mind: **(1) Is the nodule cancerous? (2) Is the nodule causing symptoms due to pressure on the adjoing structures of the neck? (3) Is the nodule making to much of thyroid harmone?**

How to perform the initial evaluation of a solitary nodule is depicted as flow chart Fig. 1.

History and examiantion : Thorough initial clinical evaluation of the patient with solitary thyroid nodule includes history of the thyroid mass, past medical history, family and social history, a careful review of systems, and a complete head and neck examination. Symptoms such as neck pain, stridor, dysphonia, and dysphagia increase clinical suspicion of a thyroid malignancy; however, none is diagnostic. Prior history of radiation exposue should be ascertained in all patients presenting with solitary thyroid nodule. Past medical history of family history of pheochromocytoma, hyperparathyroidism, chronic constipation and diarrhea, hypertension, and episodes of nervousness or excitability should alert the clinician of the possibility of familial MEN 2a or

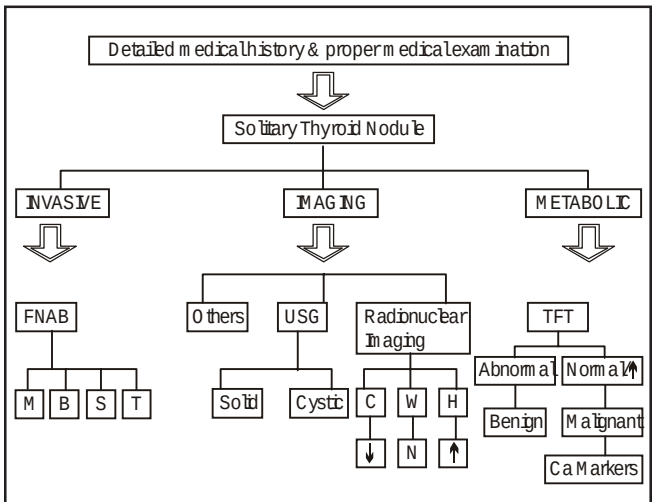

Fig. 1 : Evaluation of Solitary Thyroid Nodule

2b syndrome.

A number of features in the history and physical examination significantly influence the statistical probability of malignancy in a thyroid nodule. factors favoring malignant diagnosis include the following :(a) Age younger than 20 years or older than 70 years; (b) Male sex; (c) Associated symptoms of dysphagia or dysphonia; (d) History of neck irradiation; (e) Prior history of thyroid carcinoma; (f) Firm, hard, or immobile nodule; (g) Presence of cervical lymphadenopathy.

Factors favoring benign diagnosis include the following :

- Family history of autoimmune disease (eg, Hashimoto's thyroiditis)
- Family history of benign thyroid nodule or goiter.
- Presence of thyroid hormonal dysfunction (eg, hypothyroidism, hyperthyroidism)
- Pain or tenderness associated with nodule
- Soft, smooth, and mobile nodule
- Multinodular goiter without a dominant nodule

Physical characteristics of a thyroid nodule are poor predictors of malignancy. Both malignant and benign solitary thyroid nodules can be soft or firm, smooth or irregular on examination. However, increased size of a thyroid nodule correlates with increased risk of malignancy. Moreover, size is used in tumor staging and is highly predictive of outcome. Fixation to or invasion of surrounding structures and the presence of pappable lymph nodes in the neck are also highly suggestive of malignancy. Vocal cord paralysis is not a reliable indicator of malignancy because it can also occur in benign disorders.

Metabolic Profile and Other Markers : Thyroid function tests should be obtained as part of the initial evaluation of solitary thyroid nodule, and findings are usually normal in patients with thyroid cancer. Metabolic evidence of hyperthyroidism is more commonly associated with benign disorders such as an autonomously functioning adenoma or Hashimoto thyroiditis. A strong association exists between Hashimoto thyroiditis and primary thyroid lymphoma. Measurement of serum thyroglobulin levels is not recommended in the evaluation of solitary thyroid nodule because it is also elevated in benign thyroid disorders. Serum calcitonin and carcinoembryonic antigen (CEA) levels are usually elevated in patients with medullary thyroid carcinoma. However, serum CEA level has low specificity in the initial diagnosis of meduallary thyroid carcinoma.

Recently, DNA testing has proven to be an effective method for the diagnosis of MEN 2a and 2b syndromes. *ret* proto-oncogene in the paracentromeric region of the short arm of chromosome 10 is the site of mutation in 90% patients with familial medullary thyroid carcinoma and medullary thyroid carcinoma associated with MEN 2a and 2b. Patients with medullary thyroid carcinoma should undergo direct DNA analysis to identify possible germline mutations in the *ret* proto-oncogene. All family members should undergo similar testing if an *ret* mutation is identified. Family members with the *ret* mutation should undergo genetic counseling and be informed about prophylactic thyroidectomy.

Imaging

Ultrasonography : Ultrasonography is a safe and effective method of determining the size and the presence of solid or cystic components within a thyroid nodule. High-resolution ultrasonography can be used to determine the presence of nonpalpable nodules as small as 1mm within the thyroid tissue. Unfortunately, malignant thyroid nodules cannot be differentiated from benign thyroid nodules by this technique. Its main indications are accurate measurement of size and as a guide for FNAB.

Radionuclide imaging : The fact that malignant thyroid tissue concentrates less radioactive iodine than normal thyroid tissue is being utilized in this technique. Thyroid nodules are further classified into cold, warm, and hot according to their ability to accumulate the radioactive isotope. Cold nodules are considered hypofunctional, whereas warm nodules are normal and hot nodules are hyperfunctional. Iodine I 123 and technetium Tc 99m are the most commonly used radionuclides for thyroid imaging. The major limitation of thyroid radionuclide scanning has been its inability to distinguish between benign and malignant thyroid nodules with high accuracy. Other limitations of radionuclide scanning include an inability to delineate thyroid gland and misinterpretation of the functional status of the thyroid nodule if normal functioning thyroid tissue overlies the cold solitary thyroid nodule or if the thyroid gland is asymmetric. Therefore, radionuclide scanning is not the most accurate technique to distinguish benign from malignant thyroid disorders.

Other imaging techniques : Computed tomography scanning and magnetic resonance imaging have a limited role in the initialevaluation of solitary thyroid nodule. Indications for these imaging techniques include suspected tracheal involvement, either by invasion or compression, extension into the mediastinum, or recurrent disease. Use of intravenous iodinated contrast agent in computed tomography scanning makes thyroid scanning impossible because of the iodine load.

***Invasive Procedures :* FNAB** has become the diagnostic tool of choice for the initial evaluation of solitary thyroid nodule because of its accuracy, safety, and cost effectiveness. Although needle biopsy can be performed easily, but consistently obtaining adequate tissue and processing the specimens to achieve accurate cytopathological interpretation requires expertise and experience. A satisfactory specimen should contain at least 5 or 6 groups of 10-15 well-preserved cells. FNAB specimens are classified as

malignant, benign, indeterminate (suspicious for follicular or Hurthle cell neoplasm), or insufficient for diagnosis. Overall sensitivity, specificity, and accuracy of the FNAB technique has been reported to be 83%, 92%, and 95%, respectively.

Accuracy of FNAB is closely related to the histologic type of thyroid carcinoma that is being evaluated. Diagnosis is correct for papillary thyroid carcinoma in approximately 90-100% of FNAB specimens when correlated with the histology of the final surgical specimen. Undifferentiated (anaplastic) carcinoma, medullary thyroid carcinoma, and primary thyroid lymphoma also have characteristic cytologic features, which aid correct diagnosis in approximately 90% of FNAB specimens.

The main limitation of FNAB is the differentiation of benign from malignant follicular neoplasms. FNAB specimens of follicular neoplasms and Hurthle cells are commonly interpreted as indeterminate or suspicious. This has resulted in low FNAB accuracy rates of approximately 40% for follicular carcinomas. diagnosis of follicular carcinoma also requires the identification of capsular and/or vascular invasion, which is not a possibility with FNAB techniques. Therefore, several techniques in addition to FNAB has been developed to increase the accuracy of FNAB for follicular carcinomas, including immunocytochemistry techniques, large needle biopsy, and intraoperative frozen section analysis.

Thyroid peroxidase (TPO) immunocytochemistry with a monoclonal antibody termed MoAb 47 has been reported to significantly increase the accuracy of FNAB in patients with follicular lesions. Large needle biopsy can also increase the diagnostic accuracy of FNAB, but it also increases the risk of hematoma, tracheal injury, laryngeal nerve injury or injury to other neck structures, and cutaneous implantation of malignant cells.

Management

Management consists of observation, levothyroxine suppression therapy, or surgery. Patients with **benign solitary thyroid nodule** may undergo observation or levothyroxine suppression therapy as the initial treatment modality. *Levothyroxine* is typically administered for 6-12 months to determine if the solitary thyroid nodule decreases in size. If the nodule decreases in size after treatment with levothyroxine, this medication is discontinued, with follow-up examination of the thyroid nodule in 3-6 months. However, if a benign solitary thyroid nodule increases in size, a repeat trial of levothyroxine and repeat FNAB may be indicted. Additionally, growth of a thyroid nodule during levothyroxine therapy is a strong indication for *surgery*.

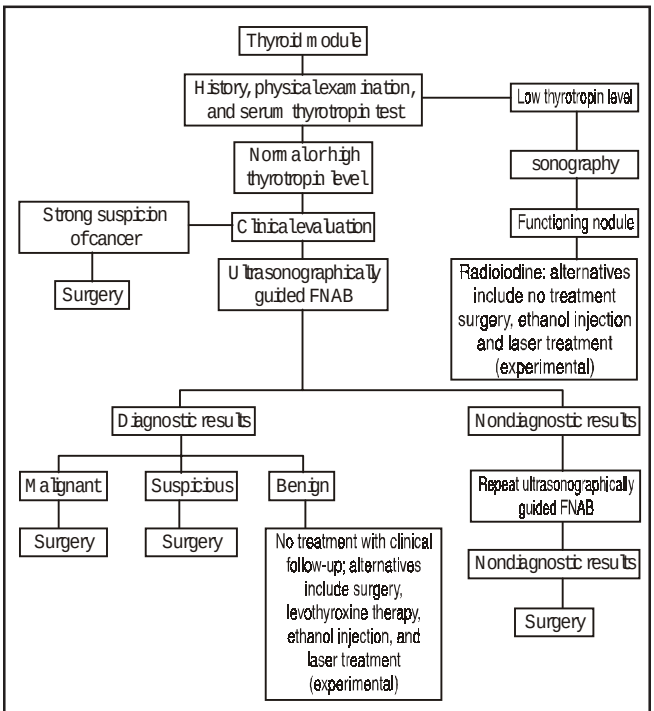

Fig.2 : Treatment plan of Thyroid nodule.

Solitary thyroid nodules that are **malignant**, suspicious, or indetrminate on FNAB require excisional biopsy in the form of thyroidectomy. Considerable controversy exists regarding the extent of surgery for malignant, suspicious, or indeterminate solitary thyroid nodules. However, principle philosophies involved in the arguments for either thyroid lobectomy or total thyroidectomy are beyond the scope of this article. A treatment plan is depicted as a flow chart Fig.2.

Recommended Reading

1. Hegedus L. The thyroid nodule. New Eng. Jr. of Medicine Oct21,2004;351:1764-1771.
2. Daniel JK, Kim M. Evaluation of thyroid nodule. eMedicine World Medical Library May 6, 2003.
3. Hebra A, Miller M. Solitary thyroid nodule eMedicine World Medical Library Nov 30, 2004.
4. Feld S, Garcia M: AACE Clinical Practice Guidelines for the Diagnosis and Management of Thyroid Nodules. 1996.
5. Singer PA: Evaluationa and management of the solitary thyroid nodule. Otolaryngol Clin North Am 1996 Aug;29(4):577-91.