Recent Modalities in Diagnosis & Treatment of Solitary Thyroid Nodule

An Essay
submitted for partial fulfillment of
Master Degree in
General Surgery

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2010

الطرق الحديثة
في
تشخيص وعلاج عقيدة الغدة الدرقية

رسالة للحصول على درجة الماجستير
فى الجراحة العامة

مقدمه من
الطبيب / ميكل صدقى نصيف يسى
بكالوريوس الطب والجراحة

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Introduction

Thyroid nodules are a common problem. They are found in 4% – 8% of adults by palpation and in 13% – 67% when ultrasound examination is used. In autopsy studies, they have a prevalence of approximately 50% ***(Burguera & Gharib, 2000)*** .

The concern with thyroid nodules is the possibility of malignancy. Thyroid cancers are rare, accounting for only 1.0% of all cancers in most populations and 0.5% of all cancer deaths ***(Hegedus , 2004)*** .

As with all assessments, a thorough history and examination is required in patients who present with a thyroid nodule. Most nodules are asymptomatic and are often discovered serendipitously by the patient or their primary medical practitioner when being examined for another problem ***(Mitchell & Parangi , 2005) .***

Thyroid carcinomas are classified according to the cell type from which they develop. The majority are nonmedullary thyroid cancers (NMTCs), which arise from the thyroid epithelial cells. These account for approximately 95% of all thyroid malignancies and are divided into four histologic subtypes: papillary (85%), follicular (11%), Hürthle cell (3%), and anaplastic (1%). Of these, 95% are sporadic tumors and the rest are thought to represent a familial origin, that is, familial nonmedullary thyroid cancer (FNMTC) ***(Sturgeon & Clark , 2005).***

Medullary thyroid cancers (MTCs) arise from the calcitonin-producing parafollicular cells of the thyroid and account for about 5% of all thyroid malignancies. In 20% they are familial and occur as part of the multiple endocrine neoplasia (MEN) syndromes ***(Sturgeon & Clark , 2005).***

Investigation of thyroid nodules should begin with assessment of the functional status of the thyroid. Tests include serum thyroid-stimulating

hormone (TSH), free thyroxine, and free tri-iodothyronine. Measurement of TSH is the most useful initial step. With the availability of highly sensitive TSH assays, it is possible to detect subtle thyroid dysfunction with this test alone ***(Gharib & Papini , 2007) .***

If the TSH is abnormal, free thyroid hormones and thyroid antibodies should be the next investigations. Thyroid antibodies such as thyroid peroxidase and antithyroglobulin antibodies are found in most patients with Graves' disease or Hashimoto's thyroiditis. TSH receptor autoantibodies are detectable in the majority of patients with Graves' disease ***(Lennard ,2006) .***

All patients who present with a thyroid nodule should undergo ultrasound evaluation of the nodule, thyroid gland, and cervical lymph nodes, if indicated. Ultrasound is an inexpensive, readily available, and noninvasive investigation. ***(Marqusee et al., 2000) .***

An ultrasound examination should focus on the size of the nodule, its composition, the presence of additional nodules, and any sonographic appearance suggestive of malignancy. Patients with multiple thyroid nodules have the same risk for malignancy as those with solitary thyroid nodules ***(Papini et al., 2002) .***

The prevalence of thyroid cancer has been shown to be similar in patients with a solitary nodule and patients with multiple nodules ***(Frates et al., 2006) .***

A nodule that is shaped more tall than wide (defined as being greater in its anteroposterior dimension than its transverse dimension) has been shown to be suggestive of malignancy ***(Kim et al., 2002) .***

Ultrasound is an accurate and sensitive imaging modality for the detection of cervical lymph node metastasis and recurrence ***(Wang et al., 2007).***

The ultrasound features of cervical lymph nodes associated with thyroid nodule carrying the highest risk for cancer include a heterogeneous echotexture,

calcifications, no hilus, a rounded appearance, cystic changes, and chaotic hypervascularity. These lymph nodes should always be biopsied even in the absence of a malignant-appearing thyroid nodule ***(Gharib & Papini , 2007).***

FNAB is the most crucial step in the evaluation of a thyroid nodule and is the procedure of choice in the workup of thyroid nodules ***(Cooper et al., 2006).***

It is able to provide specific information about the cellular composition of a nodule that directs subsequent management decisions ***(Morgan et al., 2003).***

FNAB can be performed by palpation or with ultrasound guidance. In our institution, it is performed exclusively with ultrasound guidance. This technique has been shown to decrease false negatives resulting from needle misplacement and reduce the rate of nondiagnostic smears from 15% to 3% ***(Morgan et al., 2003).***

The four categories that are commonly used to describe FNAB results and their reported incidences are: benign, 70%; indeterminate, 10%; malignant, 5%; and nondiagnostic, 15% ***(Gharib & Papini , 2007).***

A positive result of malignancy on FNAB almost certainly warrants surgery. Total thyroidectomy for Papillary thyroid cancer (PTC) is the preferred treatment option. In one landmark paper with the longest follow-up of patients with PTC , mortality and recurrence rates were compared in patients who underwent thyroid lobectomy (ipsilateral total lobectomy with isthmusectomy) versus bilateral resection (including total thyroidectomy and bilateral subtotal or near total thyroidectomy). They were able to demonstrate that, after 20 years, the rates for local recurrence and nodal metastasis were 14% and 19% after thyroid lobectomy and only 2% and 6% after bilateral resection, respectively ***(Hay et al., 1998).***

Following total thyroidectomy in patients with PTC and FTC, 131I ablation should be undertaken to destroy residual thyroid tissue, decrease the

risk for local recurrence, and facilitate long-term surveillance with whole-body iodine scans and stimulated thyroglobulin measurements . This has been shown to have the greatest benefits in patients with tumors>15 mm or those with residual disease after surgery. For patients with low-risk disease (unifocal PTC <10 mm with no extrathyroidal extension or lymph node metastasis), the benefit is more controversial, and the recommendation is to give smaller amounts of 131I ***(Mazzaferri , 2007).***

Anaplastic thyroid cancers are aggressive tumors with an extremely poor prognosis. Surgery is rarely possible because of the extent of the local disease. Radiotherapy and chemotherapy are the main modalities of treatment ***(Lennard , 2006).***

An FNAB result of "suspicious for malignancy," particularly if it is papillary, allows the use of an intraoperative frozen section diagnosis for decision making ***(Tsan et al., 2007).***

DEVELOPMENT OF THYROID

The thyroid gland is the first endocrine gland to develop, starting on approximately the 24th day of gestation *(Gabriel & scott, 2008)* .

The principle cells of the thyroid gland, which form thyroid follicles and produce thyroglobulin, arise from an endodermal bud between the first and second branchial arches, known as the *foramencecum* .The foramen cecum can be found as a blind pit in the midline of the tongue and is located between the anterior two-thirds and posterior one-third of the tongue. In adults, this border is delineated by the circumvallate papillae and corresponds to the ectodermal-endodermal boundary of the tongue. The initial thyroid primordium thickens and invaginates inferiorly, forming a tubular structure called the *thyroid diverticulum*. As it continues to descend, it becomes bilobed and solidifies until it reaches its eventual position in the inferior aspect of the anterior neck *(Gabriel & scott,2008)* .

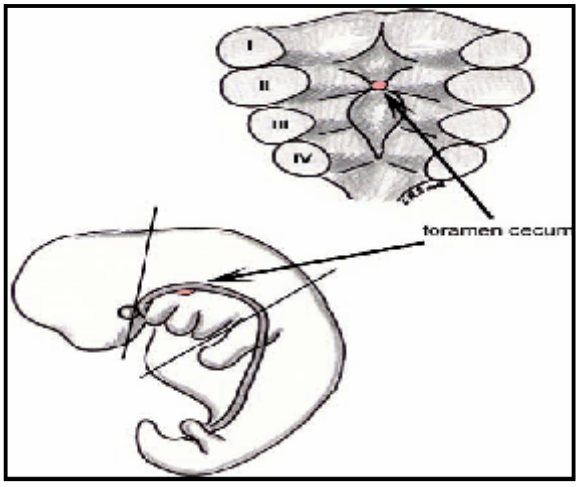

Fig 1-1 : The foramen cecum and branchial arches at 28th day of development.
(Gabriel& scott,2008)

The thyroid is dragged by the forming heart. Three thyroid transcription factors, TTF-1, TTF-2, and PAX-8, are essential for normal development and migration of the thyroid.

Mice that are homozygotes for a defect in the TTF-1 gene have no thyroid tissue and have severe defects of the hypothalamus, forebrain, and lungs. Similarly mice with homozygous defects in the Pax-8 gene have no thyroid (follicular) cells. In a proportion of TTF-2 knockout mice the thyroid is an ectopic position. This suggests that TTF-2 is required for migration of the forming thyroid.

These three factors are also involved in the production of functional proteins by follicular cells that are essential for the formation of thyroid hormones. These include the sodium iodide symporter (NIS), thyroid peroxidase (TPO), and thyroglobulin (Tg).

The midline thyroid fuses with tissues derived from the fourth and fifth branchial clefts, which combine to form the lateral lobes. These bring neuroendocrine cells from the ultimobranchial body that forms parafollicular cells (also called C cells). C cells produce and secrete calcitonin *(Van Vliet,2003)* .

The migratory route from the foramen cecum to the cervical position is called the thyroglossal tract. In early embryological formation this is a tube, the thyroglossal duct, but during embryologic development it usually becomes fibrotic, and after birth it is even difficult to identify at operation *(Kang HC,2004)* .

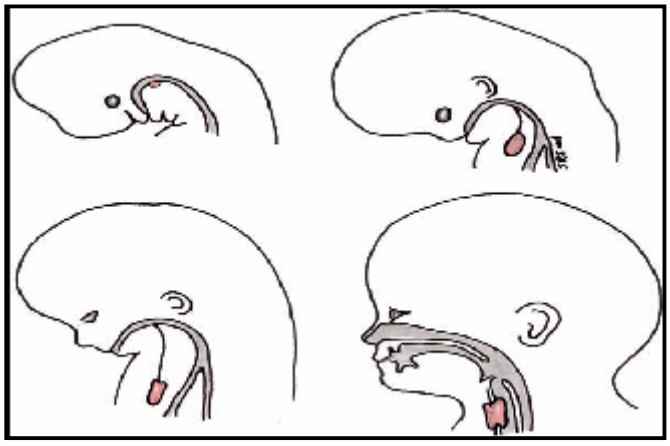

Fig 1-2 : The descent of the foramen cecum . *(Gabriel& scott,2008)*

Abnormalities in the development of thyroid

■ **The pyramidal lobe:**

Occasionally, the thyroglossal duct fails to atrophy. As a result, accessory or ectopic thyroid tissue can be found anywhere along the migratory courseof the duct. In fact, the pyramidal lobe, found in approximately 50% of the population, is actually failure of the inferior portion of the thyroid duct to involute

These foci of accessory thyroid tissue can be metabolically active, although the amount of thyroid hormone is usually insufficient without the main gland. Ectopic thyroid remnants have also been known to development malignancy, although this is uncommon. ***(Gabriel & scott,2008)***

In some patients who have had a thyroidectomy for thyroid cancer the pyramidal lobe is left, and it can be seen on scintiscan using radioactive iodine and misinterpreted as residual cancer. The pyramidal lobe usually contains normal thyroid tissue, and it is not very common for thyroid cancer to metastasize to lymph nodes in the midline superior to the isthmus. Therefore, midline tissue just cranial to the thyroid bed that traps radioiodine is usually but not necessarily benign. The clinician should review the pathology and surgical findings regarding the size and position of the primary cancer and the level of serum Tg to determine whether this is likely to be residual cancer or not ***(Peretz A.etal,2004).***

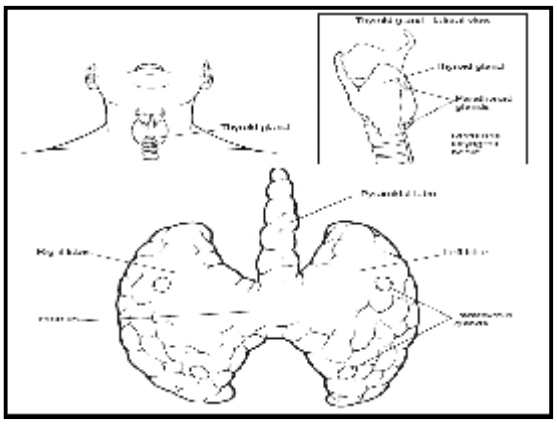

Fig 1-3 : Thyroid gland, anterior and lateral views. ***(Dominique&david,2008)***

■ **Lingual thyroid:**

Rarely the gland fails to migrate from its original site of development, resulting in a lingual thyroid, as shown in (Figure 1.4). The condition presents with a mass at the base of the tongue that can cause dysphagia, dysphonia, and dyspnea *(Gallo A.etal,2001).*

In general a maldescended thyroid does not produce physiological quantities of thyroid hormones, and the patient is hypothyroid and has an elevated thyroid stimulating hormone (TSH). One of the reasons is because the lateral lobes have not fused with the median thyroid; therefore, the volume of cells is insufficient for adequate production of thyroid hormones. In most patients with an ectopic thyroid that is the only functioning tissue, but there are exceptions, including one report where the lingual thyroid was recognized 20 years after the patient had undergone thyroidectomy for a multinodular goiter. *(Bayram F.etal,2004)*

Fig 1- 4 : A lingual thyroid in a middle-aged man.
(Ross MCDougall,2006)

The high TSH perpetuates the growth of ectopic dysfunctional thyroids. The treatment of an uncomplicated lingual thyroid is administration of thyroid hormone for life to suppress TSH.Very occasionally the mass needs to be ablated with ^{131}I *(Park HM.etal,2003)* .

Because the patients are hypothyroid it does not make sense to autotransplant the tissue since thyroid hormone will be necessary for life in any case *(Ross MCDougall,2006)* .

■ Ectopic Thyroid :

The thyroid can migrate from the base of the tongue but fail to reach its cervical position. This is a maldescended or ectopic thyroid and it usually presents as a midline swelling in the neck *(Peretz A.etal,2004).*

In about 50% of patients undergoing thyroid surgery it is possible to identify thyroid rests situated from the inferior border of the gland to the arch of the aorta. These are called thyrothymic thyroid rests *(Sackett WR.ETAL,2002).*

There are case reports of thyroid in bizarre sites such as porta hepatis, gallbladder, and vagina, and it is hard to understand how they can migrate to those sites based on our knowledge of embryology *(Khan & Nose ,2004).*

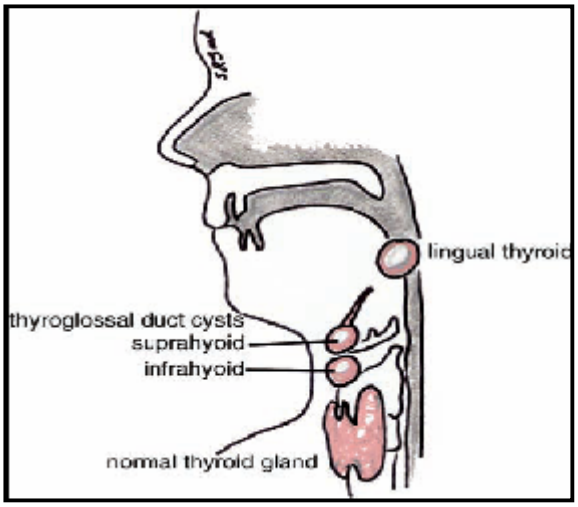

Fig 1-5 : Locations of ectopic thyroid tissue *(Gabriel& scott,2008)*

In all cases of ectopic thyroid it is important to ensure that the tissue is not a metastasis. The thyroid should be examined clinically and by ultrasound and the pathologist should look for features in the cells and their

nuclei that might indicate the tissue is malignant rather than ectopic *(Ross MCDougall,2006)* .

■ Thyroglossal Duct Cysts:

Failure to atrophy can also lead to thyroglossal duct cysts and sinuses. These lesions typically present as midline masses and are usually centered below the hyoid bone, although they may be located superiorly as well *(Organ GM& Organ CH, 2000)* .

The differential diagnosis of thyroglossal cyst is ectopic thyroid and an ultrasound is recommended to confirm that a cyst is present and that the thyroid is in the normal position, or alternatively, that the midline mass is solid and the thyroid is absent. Some authorities recommend fine needle aspiration (FNA) of all thyroglossal cysts to identify the rare cancer *(Peretz A.ETAL,2004)* .

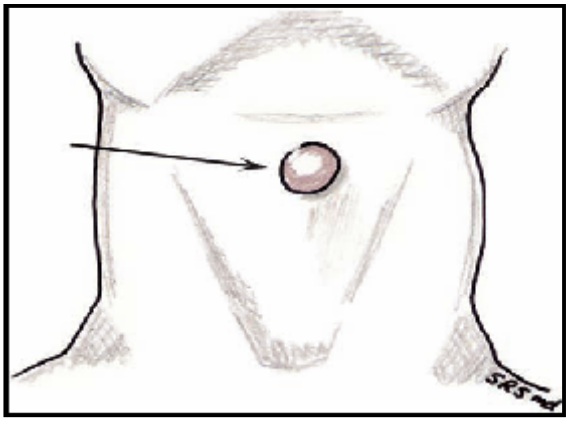

Fig 1-6 : Thyroglossal duct cyst *(Gabriel& scott,2008)*

Thyroglossal duct cysts may become infected, leading to erythema, swelling, and occasional purulent drainage if the overlying skin ruptures. Treatment consists of systemic antibiotics and possible excision. If excision is considered, removal of duct remnants is important to prevent recurrences. As the thyroglossal duct is intimately involved with the hyoid bone, removal of the central portion of the. hyoid decreases the risk of

recurrence to 1%. Some authors profess that the hyoid may be left intact if the duct is clearly noted to travel away from the bone *(Organ GM& Organ CH, 2000)* .

Gross anatomy of thyroid

The thyroid is a brownish-red and highly vascular gland located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra down to the first thoracic.

The gland varies from an H to a U shape and is formed by 2 elongated lateral lobes with superior and inferior poles connected by a median isthmus

The isthmus overlies the second to fourth tracheal rings with an average height of 12-15 mm. The isthmus is encountered during routine tracheotomy and must be retracted (superiorly or inferiorly) or divided. Occasionally, the isthmus isabsent, and the gland exists as 2 distinct lobes.

The left and right lobes cover the lower sides of the larynx and upper trachea with the superior poles diverging laterally at the level of the oblique lines on the laminae of the thyroid cartilage. The lower poles diverge laterally at the level of the fifth tracheal cartilage *(Dominique&david,2008)* .

Each lobe is pear-shaped with narrow upper pole and a broader lower pole , it is triangular in cross section with lateral ,medial and posterior surfaces.

The lateral surface is under cover of sternohyoid , sternothyroid and omohyoid muscels.The medial surface lies against the lateral side of the larynx and upper trachea and related to cricothyroid muscle,external and recurrent laryngeal nerves. The posterior surface overlaps the medial part

of the carotid sheath (the part cotaining the common carotid artery) ***(Hanks.,2001)*** **.**

The average dimension by ultrasonography of each lobe is 4 cm long vertically,1–1.5 cm wide, and 1 cm in thickness. The isthmus is usually less than 5 mm high and 3 mm deep ***(Gabriel & scott,2008)*** **.**

In certain individuals, thyroid tissue extends superiorly along the midline from the thyroid isthmus. This tissue is known as the ***pyramidal lobe*** **and represents remnants of the embryonic thyroglossal duct** ***(Gabriel & scott,2008)*** **.**

In the adult, the normal thyroidweighs 20 to 25 g ***(baskin hj,2000)*** **.**

The thyroid gland is ensheathed by the visceral fascia, a division of the middle layer of deep cervical fascia, which attaches it firmly to the laryngoskeleton. The anterior suspensory ligament extends from the superiormedial aspect of each thyroid lobe to the cricoid and thyroid cartilage. The posteromedial aspect of the gland is attached to the side of the cricoid cartilage, first and second tracheal ring, by the posterior suspensory ligament (ie, Berry ligament). This firm attachment of the gland to the laryngoskeleton is responsible for movement of the thyroid gland and related structures during swallowing ***(Dominique&david,2008)*** **.**

The lateral surface of the thyroid is covered by the sternothyroid muscle, and its attachment to the oblique line of the thyroid cartilage prevents the superior pole from extending superiorly under the thyrohyoid muscle. More anteriorly are the sternohyoid and superior belly of the omohyoid muscle, overlapped inferiorly by the anterior border of the sternocleidomastoid muscle. The sternohyoid and sternothyroid muscles are joined in the midline by an avascular fascia that must be incised to retract the strap muscle laterally in order to access the thyroid gland during thyroidectomy ***(Dominique&david,2008)*** **.**