UPDATE IN MANAGEMENT OF THE SOLITARY THYROID NODULE

Essay
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INTRODUCTION

A solitary thyroid nodule (STN) is a common problem in clinical practice. It occurs in 4-7% of adults and is usually a benign lesion ***(Alliric and Bruce, 2005).***

The solitary thyroid nodule is defined as a discrete palpable swelling in an otherwise impalpable gland ***(Russell et al., 2000).***

Palpation of a thyroid nodule should initiate a work up to exclude the possibilities of malignancy or autonomous function ***(Singer, 1998).***

Fine needle cytology is believed to be the most effective method available for distinguishing between benign and malignant thyroid nodules. However, the incidence of indeterminate specimens ranges from 4-15 % ***(Welker and Orlov, 2003).***

Radionuclide thyroid can provide functional information about nodules, differentiating between cold nodules (decreased uptake) and hot nodules (increased uptake). It does not provide information that allows a clear separation of benign and malignant nodules ***(Welker and Orlov, 2003).***

Ultrasonography can provide information about location, size and consistency of the thyroid nodule but it can not differentiate between benign and malignant nodules. It is useful in the follow-up period to identify any further nodular growth ***(Alliric and Bruce, 2005).***

Management of the solitary thyroid nodule is one of the most controversial issues ***(Bennedbaek et al., 1999).***

Malignant or suspicion of malignant cytology, associated history taking and the physical examination are the main indications of thyroidectomy ***(Alliric and Bruce, 2005).***

Recently, new modalities in the treatment of the solitary thyroid nodule have been applied as alternatives to the conventional thyroidectomy which lead to decrease the incidence of complications and rapid recovery as endoscopic thyroidectomy ***(Gagner et al., 2003)***, ultrasonography guided thermic tissue coagulation with interstitial laser photocoagulation (ILP) ***(Dossing et al., 2003),*** and percutaneous ethanol injection (PEI) ***(Pomorski and Bastos, 2002).***

PATHLOGY OF THE SOLITARY THYROID NODULE

Definition:

The solitary thyroid nodule (STN) is defined as a discrete palpable swelling within an otherwise impalpable gland ***(Russell et al., 2000).***

Incidence:

The solitary thyroid nodule occurs in 4-7% of all population and it is usually a benign lesion ***(Alliric and Bruce, 2005).*** In a study on 200 patients investigated for thyroid diseases reported 36 percent of these patients were found to have a solitary nodule of the thyroid. However, Approximately 23 percent of solitary thyroid nodules are actually dominant nodules within a multinodular goiter ***(Walsh et al., 1999).***

Relation to age and sex:

Single nodules are about four times more common in women than in men. It increases in prevalence with an advancing age ***(Peter, 1996).***

Causes of the solitary thyroid nodule:

Any thyroid disease can present as a solitary thyroid nodule ***(Mahmood and Ernest, 1998).*** The most significant causes include ***(Welker and Orlov, 2003):***

I- Non neoplastic:

1. Adenomatous (colloid) nodule.
2. Autonomous toxic nodule.

3. Cyst.
4. Developmental abnormalities.
    a. Thyroglossal cyst.
    b. Thyroid hemiagenesis.

5. Inflammatory thyroid disorders:
    a. Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis).
    b. Subacute thyroiditis (De Quervain's disease).
    c. Fibrous (Riedel's) thyroiditis.

II- Neoplastic:

A- Benign nodules:

1. Follicular adenoma:
    a. Macrofollicular (colloid) adenoma.
    b. Microfollicular (fetal) adenoma.
    c. Trabecular (embryonal) adenoma.
    d. Hurthle cell adenoma.
2. Papillary adenoma.

B- Malignant nodules:

1. Papillary carcinoma.
2. Follicular carcinoma.
3. Hurthle cell carcinoma.
4. Medullary carcinoma.
5. Undifferentiated (anaplastic) carcinoma.
6. Thyroid lymphoma.
7. Teratoma.
8. Secondary (metastatic) tumor.

I- Non neoplastic causes presenting as STN:

1- Adenomatous (colloid) nodule:

Incidence:

This represents about 60-70% of STN's ***(Al-sayer et al., 1985).***

Pathology:

The deficiency in the thyroid hormone production induced by iodine deficiency leads to increase in thyroid stimulating hormone (TSH) secretion, which results initially in a hyperactive thyroid with tall follicular epithelium and small amounts of colloid. Later on, follicular atrophy with massive storage of colloid occurs ***(Rosai, 1996).***

Microscopically, the nodules may be uncapsulated or partially encapsulated but complete encapsulation is not present. The follicles are dilated and filled with abundant colloid. The cellularity varies; in some nodules cellularity is not increased, and the follicular epithelial cells have a flattened appearance ***(Figure1);*** other nodules may have increased cellularity ***(Bruce et al., 1997).***

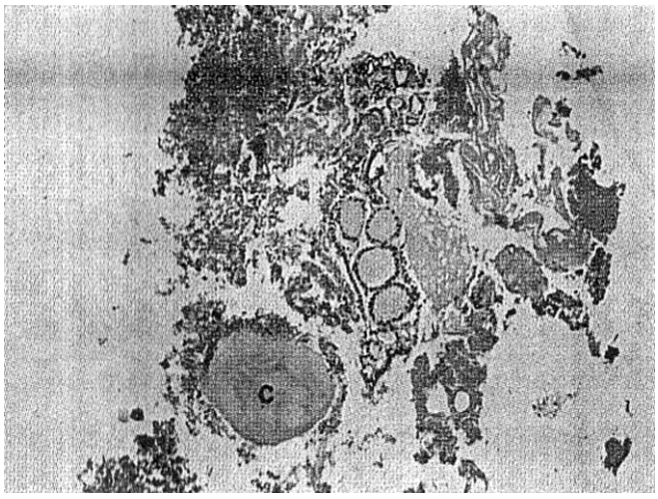

Figure (1): Adenomatous (colloid) nodule with colloid follicles of varying sizes, as well as free colloid **(Peter, 1996).**

2- Autonomous toxic solitary thyroid nodule:

Incidence:

Approximately 10% of STN's have an autonomous function ***(Miller et al., 1985).***

Pathology:

The term refers to an adenoma present in the thyroid gland that is otherwise intrinsically normal. These lesions are independent from TSH control and are able to produce thyroid hormone in large quantities ***(Rosai, 1995).*** The adenoma may undergo central necrosis and hemorrhage. As a result, the thyrotoxicosis may be relieved and the remainder of the thyroid may resume its normal function ***(Hamburger and Hamburger, 1985).***

Microscopically, it shows signs of hyperactivity, such as tall epithelium and irregularly shaped follicles with papillary projections ***(Caracangiu and DeLellis, 1996).***

3- Thyroid cyst:

Incidence:

15-25 percent of all thyroid nodules are cystic ***(Mazzaferri, 1993).***

Pathology:

Although the term cyst implies a benign process, this is far from true. A thyroid cyst may be one of several pathologic conditions including congenital, developmental or neoplastic. Virtually, all cysts arise from benign nodular masses undergoing degenerative and cystic changes ***(Bloodworth, 1982*)**; however, ***John (1990)*** reported 4% incidence of simple true epithelium lined cysts. Cysts may contain clear yellowish serous fluid or chocolate brown thick fluid ***(Miller et al., 1985).*** Malignancy is often stated to be uncommon in cysts. Papillary carcinoma may occasionally be cystic ***(John, 1990).***

4- Developmental abnormalities:

Some developmental abnormalities appear as solitary thyroid swellings. These abnormalities usually occur in the midline of the neck as a thyroglossal cyst. These lesions are cephalad to the thyroid gland and move with deglution or with protrusion of the tongue ***(Clark, 1985).*** Rarely, thyroid hemiagensis may cause hypertrophy of the controlateral lobe with a presentation of STN ***(Piera et al., 1986).***

5- Thyroiditis presenting as STN:

A- Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis):

It is also known as lymphocytic thyroiditis, autoimmune thyroiditis or goitrous autoimmune thyroiditis ***(Rosai, 1995).***

Incidence:

Hashimoto thyroiditis occasionally presents as a STN ***(Hoffman et al., 1972).*** The disease is 15 times more common in women with a peak incidence between 40 to 60 years of age ***(Alliric and Bruce, 2005)*.**

Pathology:

The disease is clearly immunomediated. Thyroid peroxidase (TPO) antibodies are detectable in up to 90% of adult patients whereas, thyroglobulin antibodies are less sensitive and are not usually recommended to document the diagnosis. Unfortunately the yield of antibodies in young patients is unpredictable and many elderly patients will have detectable antibodies with no other clinical manifestations of the disease. Negative antibody tests do not exclude any subtype of autoimmune thyroid disease ***(Joseph and Thomas, 2003*)**. Grossly, it presents as a diffuse firm enlargement of the thyroid gland without fixation to the surroundings ***(Valpe, 1978*)**.

Microscopically, two main criteria are present; lymphocytic infiltration of the stroma and oxyphilic change of the follicular epithelium. Lymphoid tissues show large follicles with prominent germinal centers lined by variable sized Hurthle cells also known as Oxyphil cells. Plasma

cells, histiocytes and scattered intrafollicular giant cells can be present ***(Figure 2).*** Connective tissue is scanty but, in the fibrous variant fibrosis is extensive with dense hyaline type not extending beyond the thyroid capsule. When fibrosis is associated with squamous metaplasia, it stimulates neoplastic changes ***(Valpe, 1978).***

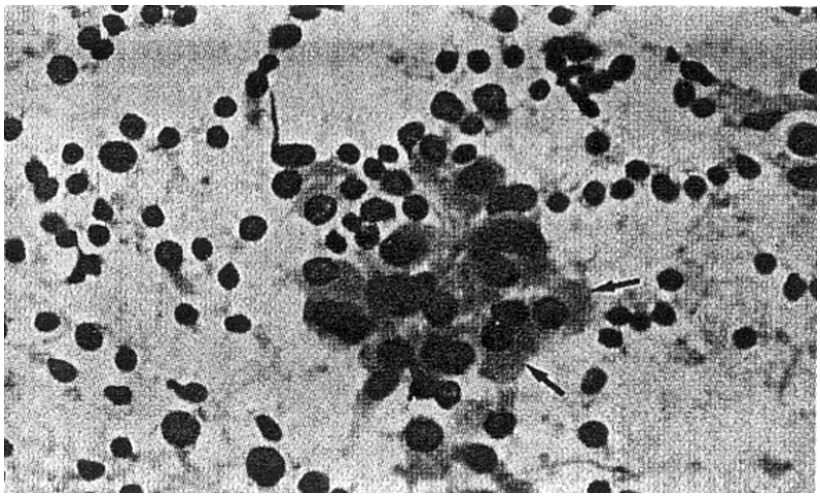

Figure (2): Hashimoto's thyroiditis with a large number of lymphocytes and Hurthle cells (arrows) ***(Peter,1996).***

B- Subacute thyroiditis (De Quervain's disease):

Incidence:

It is most common between the ages of 30 and 50 years, and affects women more than men (3-5:1) ***(John, 1990).***

Pathology:

The exact etiology is unknown. Subacute thyroiditis can occur either in painful or painless form. Painful thyroiditis is thought to be viral in origin while painless thyroiditis is considered to be autoimmune in origin that may occur sporadically or in the postpartum period. Microscopically, there is destruction of follicular epithelium, with infiltration by neutrophils, histiocytes and multinucleated giant cells. Areas of fibrosis are also seen, usually in a patchy distribution. All these surround the colloid producing atypical granulomatous appearance ***(John, 1990).***

C- Fibrous (Riedel's) thyroiditis:

Incidence:

It is a rare progressive inflammatory condition of the thyroid gland. The majority of cases occur in women around the fifth decade of life ***(Joseph and Thomas, 2003).***

Pathology:

The etiology of the disease is unclear, but the presence of circulatory thyroid antibodies in a large portion of patients favors an autoimmune pathogenesis ***(Bruce et al., 1997).*** It seems to be associated with diffuse fibrotic processes ***(Joseph and Thomas, 2003).*** It has been reported to occur with other autoimmune diseases, such as pernicious anemia and Graves' disease ***(Geeta and Orlo, 2005).***

Microscopically**,** fibrous tissue which is frequently extensive and hyalinized is found to replace the normal thyroid structure and extend from the thyroid capsule into adjacent muscles and trachea. Riedel's thyroiditis is difficult to be differentiated from carcinoma ***(Woolner et al., 1987).***

II- Neoplastic causes presenting as STN:

A- Benign neoplasms:

1- Follicular adenoma:

It is a benign encapsulated tumor composed of follicular cells ***(Rosai, 1995)***.

Incidence:

It is a common benign tumor of the thyroid gland. It occurs at any age but mainly in young adults. It is about 5 times more common in females than in males ***(Frassila, 1990).***

Pathology:

a. **Macrofollicular (colloid) adenoma:** It is composed of large follicles that are distended with colloid. Such adenomas are often indistinguishable microscopically from a colloid nodule in a multinodular goiter (***Ritchie, 1990).***

b. **Microfollicular (fetal) adenoma:** It is composed of microfollicles separated by abundant interfollicular loose connective tissue ***(Vinay et al., 1992).***

c. **Trabecular (embryonal) adenoma:** It resembles an embryonal thyroid gland in the early stage of its development. It consists of columns of small, regular epithelial cells closely packed, or with abundant and edematous stroma. Follicles are few and small, and contain little or no colloid ***(Ritchie, 1990)***.

d. **Hurthle cell adenoma:** It's composed of cells that have abundant oxyphilic cytoplasm and usually a trabecular growth pattern but may also occur in solid groups or rarely form follicles. The nuclei are enlarged and vary in size. Hurthle cells are larger than those of normal thyroid cells and are characterized by a finely granular eosinophilic cytoplasm and usually the nuclei are vesicular ***(Figure 3*)**. These adenomas show poor or absent follicular development and contain little or no colloid ***(John, 1990)*.**

2- Papillary adenoma:

This lesion, although, classified as an adenoma, is typically uncapsulated nodule with papillary formation, merges in the adjacent tissues ***(Vinay et al., 1992)*.**

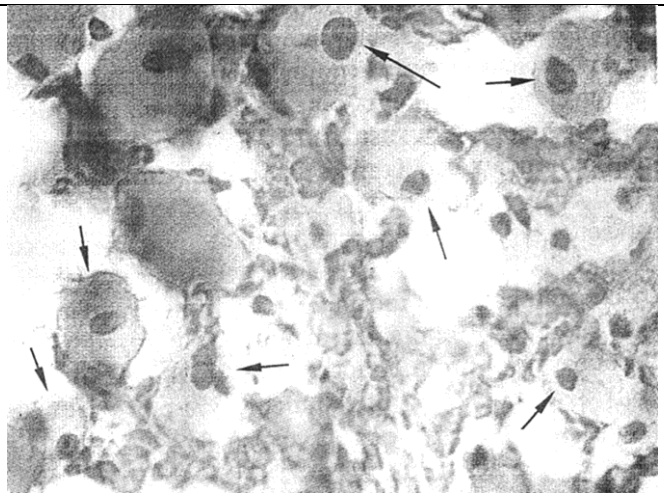

Figure (3): Hurthle cell tumor. Large single polygonal cells are visible (arrows) with abundant granular cytoplasm and uniform eccentric nuclei with prominent nucleoli, and no colloid **(Ernest, 1993).**

B- Malignant neoplasms:

Thyroid cancer is not a common disease. It accounts for less than 1% of all malignancies ***(Geeta and Orlo, 2005).*** The overall incidence of malignancy in STN is approximately 5% ***(Sanziana, 2003).*** The major subtypes of thyroid carcinoma and their relative frequencies include: papillary carcinoma (75 to 85%); follicular carcinoma (10 to 20%); medullary carcinoma (5%); and anaplastic thyroid carcinoma (< 5%) ***(Ramzi et al., 1999).***

1- Papillary carcinoma:

Incidence:

Papillary carcinoma is the commonest type of thyroid malignancy. Females are more affected than males (3:1). It can occur in any age group, the mean age at the time of initial diagnosis is about 40 years ***(Cady and Rossi, 1998).***

Pathology:

a. The tumor presents as a solitary firm or hard nodule, whitish and clearly invasive. Most papillary carcinomas are not encapsulated and may be multicentric. Less than 10% are surrounded by complete capsule. Marked cystic changes are seen in 10% of cases. Papillae are complex branching with a central fibrovascular core and single lining of cubical cells. Stroma of papillae are edematous or hyaline and may contain lymphocytes, macrophages and haemosiderin ***(Rosai, 1995)*.**

b. The nuclei of papillary carcinoma cells have the following features: (1) nuclear membrane irregularities that manifest as indentations, pseudonuclear, or nuclear grooves; (2) overlapping and enlarged nuclei; and empty appearance of the nuclei that seem pale resembling "Orphan Annie's eyes" ***(Ryan et al.,, 2003).***

c. "Psammoma bodies" which are concentrically calcified structures that are located in the papillary stalk, fibrous stroma at the tip of the papillae or between the tumors cells ***(John, 1990)***. These structures are present in 50 percent of cases ***(Ryan et al., 2003)*** and diagnostic of papillary Carcinoma ***(Ramzi et al., 1999)***.

d. Lymphocytic infiltration is found in a fourth of cases and may resemble chronic lymphocytic thyroiditis ***(Caracangiu et al., 1985)*.**

e. Papillary cystadenocarcinoma ***(Hughes et al., 1996).*** The term Papillary carcinoma is applied to any thyroid malignancy that has "pure" papillary or mixed papillary and follicular architecture or composed of cells having "ground-glass" optically clear nuclei, whether papillary formation is present or not ***(Vinay et al., 1992)*.** Mixed papillary-follicular tumor and follicular variants of papillary carcinoma are classified as papillary carcinoma ***(Geeta and Orlo, 2005)*.**

Prognosis:

Papillary carcinoma has an excellent prognosis with 10 years survival about 80-90% ***(Hundahl et al., 1998)*.** Unfavorable indications are extrathyroid extension, multicentricity and distant metastases at the time of presentation ***(Vinay et al., 1992)***.

2- Follicular carcinoma:

Incidence:

It accounts 10% of all thyroid cancers and more common in females. It is rare before the age of 30 years ***(Alliric and Bruce, 2005).***

Pathology:

Follicular carcinoma is well circumscribed and sharply demarcated from adjacent parenchyma like adenomas. This invasive nature is not always evident to the naked eye. The cut surface shows fleshy consistency, hemorrhage, necrosis and calcification **(Kini, 1987).** The major feature of follicular carcinoma is capsular or vascular invasion or both, by follicular cells ***(Figure 4*****),** which distinguishes it from follicular adenoma ***(Milikowski and Berman, 1997).*** The follicular carcinomas have been subdivided into minimally invasive and widely invasive forms ***(Rosai, 1996)*****:**

a-*Minimally invasive form:*

Grossly, it is the same as that of follicular adenoma. Microscopically, it has an evidence of microscopic invasion through the tumor capsule and or invasion into small to medium sized vessels in or immediately outside the capsule, but not within the tumor ***(Geeta and Orlo, 2005).***

b- Widely invasive form:

It demonstrates evidence of large vessels invasion and/or areas of tumor invasion through the capsule ***(Geeta and Orlo, 2005).***

Prognosis:

The cumulative percentage of patient mortality from follicular cancer is about (15%) at 10 years and (30%) at 20 years. Factors that significantly worsen long term prognosis are; (1) age over 50 years at presentation,(2) tumor size greater than 9 cm,(3) higher tumor grade,(4) marked vascular invasion and (5) extra thyroidal invasion and distant metastasis at the time of presentation ***(Sadler and Clark, 1999)***.

3- Hurthle cell carcinoma:

It accounts for approximately 3% of all thyroid malignancies ***(Hundahl et al., 1998).*** Some consider the Hurthle cell carcinoma a subtype of follicular thyroid carcinoma as it's characterized by vascular or capsular invasion. It differs from follicular carcinoma in that; it contains sheets of eosionphilic cells packed with mitochondria, more often multifocal and bilateral. It is more likely to metastasize to local nodes and distant sites and associated with higher mortality rate ***(Geeta and Orlo, 2005).***

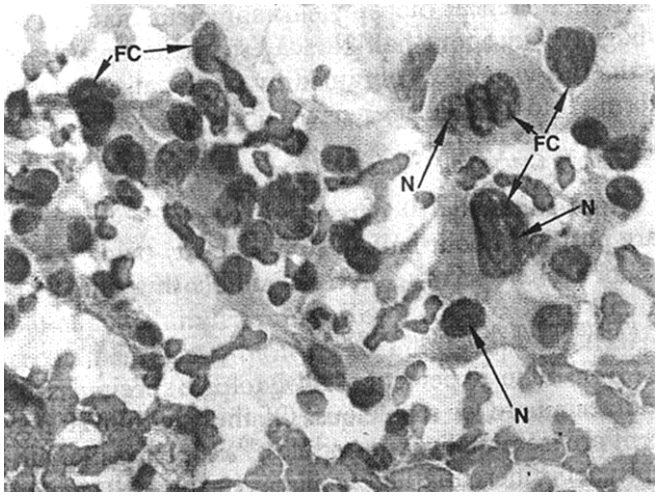

Figure (4): A follicular carcinoma containing isolated follicular cells (FC) with enlarged, variable sized nuclei, prominent nucleoli (N), coarse chromatin, and abundant cytoplasm, and no colloid **(Ernest, 1993).**

4- Medullary thyroid carcinoma (MTC):

Incidence:

Medullary carcinomas account for about 5% of all thyroid malignancies. Women and men are equally affected by medullary carcinomas ***(Geeta and Orlo, 2005).***