



Endocrine



Title: Sheet 4 – Thyroid Diseases 2

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Thyroid Diseases 2

**The underlined sentences are found in slides but not mentioned by the doctor. The time when topics were explained by the doctor in the video was added between [].*

In this lecture we will continue talking about some Thyroid diseases such as: graves' disease, diffuse and multinodular goiter, thyroid neoplasms and papillary carcinoma of the thyroid gland.

IV. Graves' Disease [0:26]

- Is the most common cause of endogenous hyperthyroidism.
- It is characterized by a triad of manifestations:
 1. **Thyrotoxicosis**: caused by a diffusely enlarged, hyperfunctional thyroid present in all cases. It's considered as the most common manifestation, 100% present of all cases.
 2. **Infiltrative ophthalmopathy** with resultant exophthalmos, present in about 40% of patients.
 3. **Infiltrative dermopathy** (sometimes designated pretibial myxedema), seen in a minority of cases.
 - Graves' disease has a peak incidence between 20 and 40 years of age, with women being affected up to seven times more commonly than men.

Pathogenesis [1:46]

- Many manifestations of Graves' disease are caused by autoantibodies to TSH:
 1. **Thyroid stimulating immunoglobulin**: this IgG antibody binds to the TSH receptor and mimics the action of TSH, causing increased release of thyroid hormones.
 - Almost all individuals with Graves' disease have detectable amounts of this autoantibody, which is relatively **specific for Graves' disease**.
 2. **Thyroid growth stimulating immunoglobulin**: directed against the TSH receptor, these antibodies have been implicated in **the proliferation of thyroid follicular epithelium increasing the growth of the thyroid gland**.
 3. **TSH binding inhibitor immunoglobulin**: These anti-TSH receptor antibodies prevent TSH from binding to its receptor on thyroid epithelial cells, and in doing so, may inhibit thyroid cell function.

Pathogenesis of infiltrative ophthalmopathy (exophthalmos):

- There is *increase in the volume of retro-orbital connective tissue* (tissues behind eyes) and extraocular muscles due to:

(1) marked infiltration of the retro-orbital space by mononuclear cells and inflammatory cells ,predominantly *T cells*, since Graves' is an autoimmune disease.

(2) Inflammatory edema and swelling of extraocular muscles.

(3) Accumulation of *glycosaminoglycans*, such as hyaluronic acid and chondroitin sulfate

(4) Increased numbers of adipocytes (fatty infiltration).

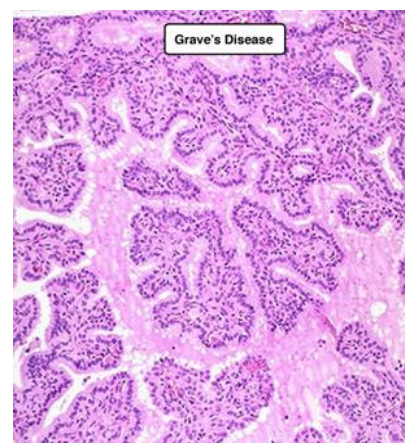
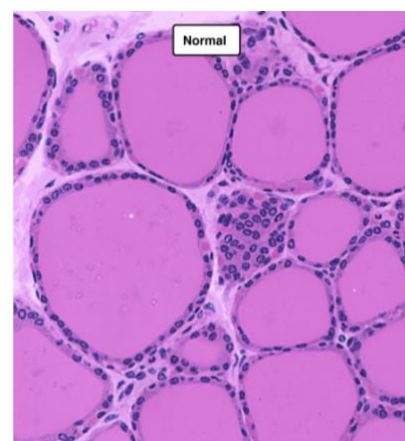
- These changes displace the eyeball forward, causing exophthalmos/ophthalmopathy, and potentially interfering with the function of the extraocular muscles.

Morphology [6:26]

- In the typical case of Graves' disease, the thyroid gland is enlarged (usually symmetrically) due to diffuse hypertrophy and hyperplasia of thyroid follicular epithelial cells.

- On microscopic examination, the follicular epithelial cells in untreated cases are *tall, columnar and more crowded than usual*.

-Lymphoid infiltrates is present throughout the interstitium (the stroma between the follicular cells) because it's an autoimmune disease.



Extra figure – added for clarification

The clinical manifestations [6:57]

- Manifestations Include those common to all forms of thyrotoxicosis: nervousness, hot flushed skin, tachycardia, irritability, tremors, and proximal myopathy.

- And those associated uniquely with Graves' disease: **ophthalmopathy** is specific to Graves' disease and not present in other causes of exophthalmos.

-Sympathetic over-stimulation of *levator palpebral muscle* produces a characteristic wide, staring gaze and lid lag and which are not specific to Graves' disease.

- The ophthalmopathy of Graves' disease results in abnormal protrusion of the eyeball (exophthalmos).
- The exophthalmos may persist or progress despite successful treatment of the thyrotoxicosis, sometimes resulting in corneal injury.
- The infiltrative dermopathy most commonly involves the skin overlying the shins, where it manifests as scaly thickening and induration of the skin (pretibial myxedema).



Exophthalmos (protrusion of the eyeball forward) – a characteristic of Graves' disease not present in other types of thyrotoxicosis, present in 40% patients with graves' disease



Pretibial myxedema – a feature of Graves' disease but seen in minority of patients, these skin lesions are present in front of tibia (pretibial) and contain large amounts of glycosaminoglycan (myxedema) that's why they are called this way. It shows with red and scaly skin.

Laboratory findings in Graves' disease include: [8:51]

- Elevated serum free T4 and T3 and depressed serum TSH.
- Because of ongoing stimulation of the thyroid follicles by TSIs, radioactive iodine uptake is increased diffusely.

V. DIFFUSE AND MULTINODULAR GOITER [9:18]

- Enlargement of the thyroid gland, or goiter, is the most common manifestation of thyroid disease.
- Diffuse and multinodular goiters are the result of impaired synthesis of thyroid hormones most often caused by dietary iodine deficiency.
- Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH, which drives the hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, enlargement of the thyroid gland (goiter).

- These compensatory changes overcome the hormone deficiency and maintain an euthyroid metabolic state in the vast majority of affected individuals.
- If the underlying disorder is severe (e.g., a congenital biosynthetic defect), the compensatory responses may be inadequate to compensate the hormones deficiency, resulting in goiterous hypothyroidism.

Pathogenesis [10:40]

- Goiters can be *endemic* or *sporadic*.

1. **Endemic goiter:** occurs in geographic areas where the diet contains little iodine.

- The designation endemic is used when goiters are present in more than 10% of the population in a given region.

- Such conditions are common in mountainous areas of the world including the Himalayas and the Andes.

- With increased availability of dietary iodine supplementation, the frequency and severity of endemic goiter have declined significantly

2. **Sporadic goiter:** occurs less frequently than endemic goiter.

- The condition is more common in females than in males, with a peak incidence in puberty or young adulthood, when there is an increased physiologic demand for T4.

- Sporadic goiter may be caused by several conditions including:

a. the excessive ingestion of substances that interfere with thyroid hormone synthesis, such as calcium and vegetables such as cabbage and cauliflower.

2.Sporadic goiter: In other instances, goiter may result from inherited enzymatic defects that interfere with thyroid hormone synthesis (dyshormonogenetic goiter)

- Note: in most cases, however, the cause of sporadic goiter is not apparent.



Goiter gross appearance – the glands contain many nodules that might show hemorrhage and fibrosis, notice the enlargement of the glands

Clinical Features [12:55]

- The dominant clinical features of goiter are those caused by the mass effects of the enlarged gland causing:

a. Cosmetic problem of a large neck mass

b. Goiters also may cause airway obstruction, dysphagia (compression of esophagus), and compression of large vessels in the neck and upper thorax (so-called superior vena cava syndrome), might cause dyspnea (difficulty of breathing)

- Note: multinodular goiters typically are hormonally silent so the patients are euthyroid.
- A minority (approximately 10% over 10 years) manifest with thyrotoxicosis secondary to the development of autonomous nodules that produce thyroid hormone independent of TSH stimulation.
 - This condition, known as toxic multinodular goiter or Plummer syndrome, is not accompanied by the infiltrative ophthalmopathy and dermopathy of Graves' disease-associated thyrotoxicosis.
- The incidence of malignancy in long-standing multinodular goiters is low, (<5%) but not zero. The concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms (e.g., hoarseness of the voice due to invasion of the vocal cords).

VI. THYROID NEOPLASMS [15:06]

- From a clinical standpoint, the possibility of a tumor is of major concern in patients who present with thyroid nodules.

- Fortunately, the overwhelming majority of solitary nodules of the thyroid prove to be either: *a. benign adenomas (follicular adenoma)*

Or *b. Localized, non-neoplastic conditions (e.g., a dominant nodule in multinodular goiter, simple cysts, or foci of thyroiditis).*

- Carcinomas of the thyroid, are uncommon, accounting for less than 1% of solitary thyroid nodules.

- Several clinical criteria provide a clue to the nature of a given thyroid nodule:

1. Solitary nodules, in general, are more likely to be neoplastic than are multiple nodules.
2. Nodules in very young <20 years or very old more than 70 years' individuals are more likely to be neoplastic.
3. Nodules in males are more likely to be neoplastic than are those in females.
4. A history of radiation exposure of the head and neck is associated with an increased incidence of thyroid malignancy.

5. Nodules that uptake radioactive iodine in imaging studies (hot nodules) are more likely to be benign.

Follicular Adenomas [17:25]

- Are benign neoplasms, derived from the lining follicular epithelium of the follicles of the thyroid gland.
- Follicular adenomas usually are solitary.
- On clinical and morphologic grounds, they are difficult to diagnose because they may be difficult to distinguish from a dominant nodule in multinodular goiter, or from less common follicular carcinomas (the malignant counterpart of those lesions).
- Sometimes, they might only be differentiated from follicular carcinomas through microscopic examination, and even microscopic examination might fail to do so.
- Although the vast majority of adenomas are nonfunctional (don't produce any thyroid hormones), a small proportion produce thyroid hormones called toxic adenomas (toxic nodules/hot nodules), causing clinically apparent thyrotoxicosis.



This figure shows the gross appearance of follicular adenoma. The red tissue is the normal thyroid tissue and the one surrounded by a white capsule is the follicular adenoma. As you can notice, this mass is solitary, not multiple.

It's important, by microscopic examination, to examine the capsule. If there is infiltration in the capsule by neoplastic cells, it's then follicular carcinoma. So, microscopic examination is necessary.

Thyroid Carcinomas [19:56]

- A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years.
- By contrast, cases seen in childhood and late adult life are distributed equally between males and females.
- Most thyroid carcinomas (except medullary carcinomas which arise from the c-cells: calcitonin secreting cells) are derived from the thyroid follicular epithelium.

Subtypes of thyroid carcinomas

- The major subtypes of thyroid carcinoma and their relative frequencies are:
 - a. Papillary carcinoma (accounting for more than 85% of cases) – most common type.

- b. Follicular carcinoma (5% to 15% of cases) – second most common type.
- c. Anaplastic (undifferentiated carcinoma (<5% of cases)).
- d. Medullary carcinoma (5% of cases) arising from c-cells, not follicular cells.

Environmental Factors [21:25]

1. The major risk factors predisposing to thyroid cancer is exposure to ionizing radiation, particularly during the first 2 decades of life.
 - There was a marked increase in the incidence of papillary carcinomas among children exposed to radiation as treatment for malignant tumors, such as lymphomas.
2. Deficiency of dietary iodine (and by extension, an association with goiter) is linked with a higher frequency of follicular carcinomas.

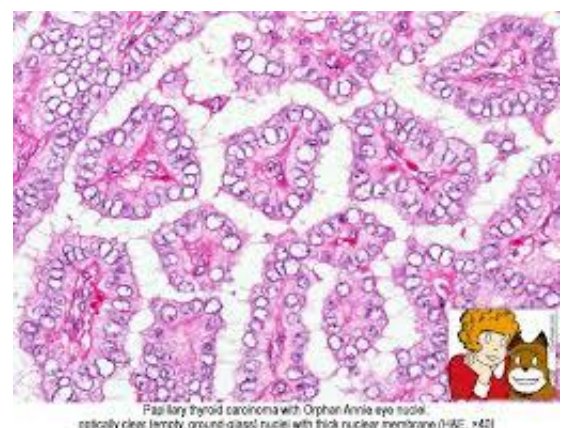
I. Papillary Carcinoma

- Papillary carcinomas are the most common form of thyroid cancer (it accounts for more than >85% of the thyroid carcinoma).
- They could occur at any age.
- They account for the vast majority of thyroid carcinomas associated with previous exposure to ionizing radiation in childhood [eg: head and neck tumors treatment such as lymphomas.](#)

MORPHOLOGY [23:10]

- Papillary carcinomas are solitary or multifocal lesions.
- Some tumors may be well circumscribed and encapsulated from the adjacent tissues, while others infiltrate the adjacent parenchyma of the neck.
- The microscopic hallmarks of papillary neoplasms include the following:
 - a. Branching papillae having a fibro vascular stalks covered by a single to multiple layers of neoplastic cuboidal epithelial cells.

Extra figure – added for clarification



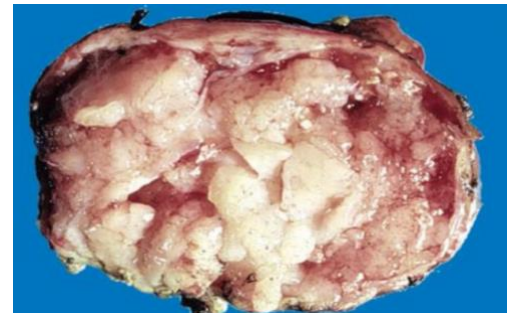
b. *Nuclei are optically clear imparts empty appearance called ground glass or Orphan Annie eye nuclei.* c. *Intranuclear inclusions ("pseudo-inclusions") – invasion of parts of the cytoplasm to the nucleus.* d. *Intranuclear grooves.*

- *Note: These nuclear features are sufficient for the diagnosis of papillary carcinoma, even in the absence of papillary architecture.*

e. Concentrically dystrophic calcified structures termed psammoma bodies.

f. Foci of lymphatic invasion by tumor are often present, but involvement of blood vessels is relatively uncommon.

- Metastases to adjacent cervical lymph nodes occur in one-half of cases.



Gross appearance of papillary carcinoma that shows many papillary projections in this tumor

Clinical Features [27:36]

- Papillary carcinomas are nonfunctional tumors.

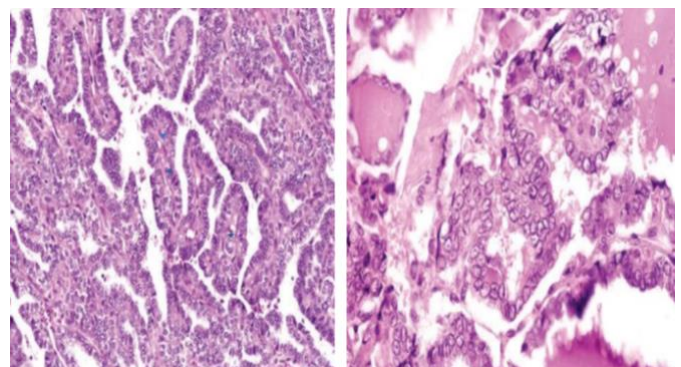
- Manifest most often as a painless mass in the neck, either within the thyroid or as a metastasis in a cervical lymph node.

- Are indolent lesions, with 10-year survival rates in excess of 95% of the cases.

- The presence of isolated cervical node metastases does not have a significant influence on prognosis.

- In a minority of patients, hematogenous metastases are present at the time of diagnosis, most commonly to the lung. - The long-term survival of patients with papillary thyroid cancer is dependent on several factors, including:

Demonstration of microscopic appearance of papillary carcinoma



- *The picture on the left shows the papillary projections which are fibrovascular cause lined by the malignant cells*
- *The picture on the right shows some of the nuclear features of the papillary carcinoma [presence of orphan annie nuclei (optically clear nuclei)]*

a. *age (the prognosis is less favorable among patients older than 40 years of age).*

b. *presence of extrathyroidal extension.*

c. *presence of distant metastases (stage) [metastasis = bad prognosis].*