Lecture One

Hypo and Hyperthyroidism and Hashimoto's thyroiditis

*432 **Pathology** Team*

***Done By: Eman** Al-Bediea & **Raghad** Al-Mutlaq*

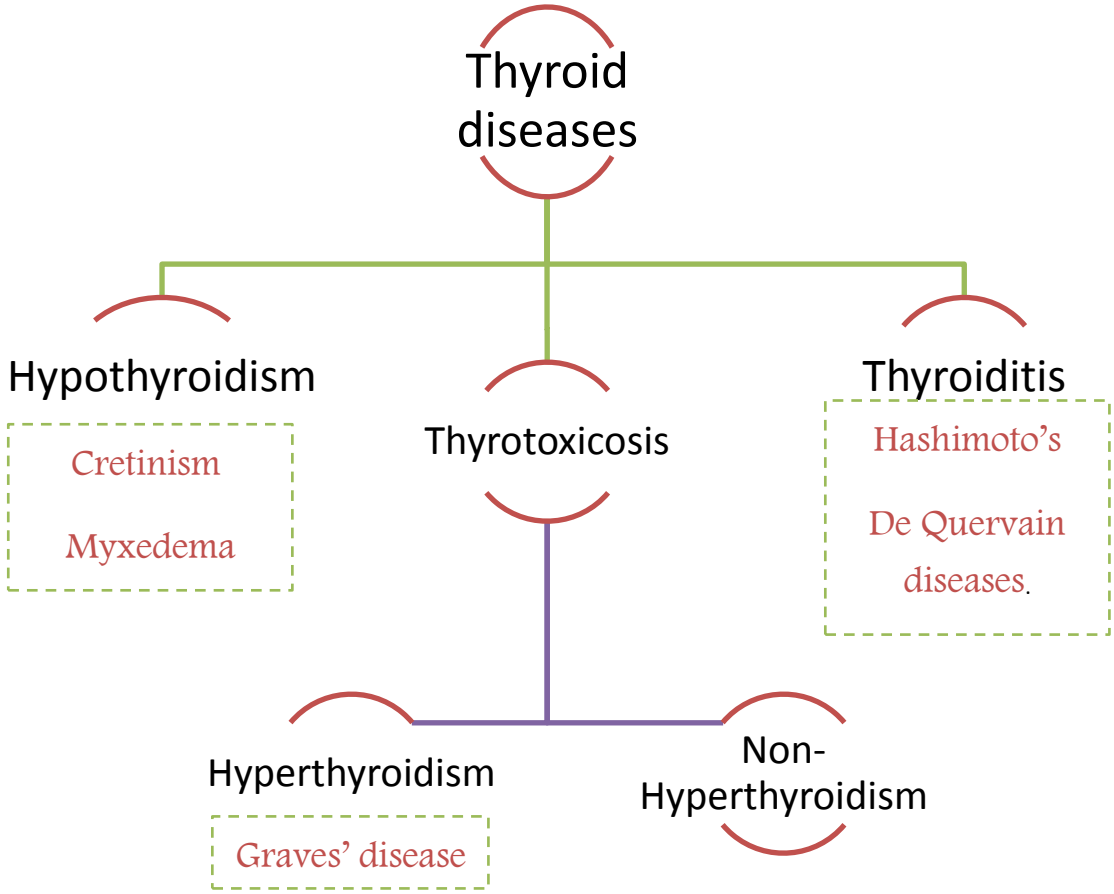
***Reviewed By: Ammar** Al-Yamani*

Endocrine Block

Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Thyroid disorders

Mind Map:



Thyroid gland

Introduction

The thyroid gland is one of the most responsive organs in the body and contains the largest store of hormones of any endocrine gland.
Secretion of thyroid hormones (T_3, T_4) which are controlled by factors secreted by hypothalamus and anterior pituitary. Low levels of T_3, T_4 stimulate the release of thyrotropin-releasing hormone (TRH) (hypothalamus) and thyroid-stimulating hormone (TSH) (anterior pituitary), causing T_3, T_4 levels to rise. Elevated T_3 and T_4 levels, in turn, negatively feedback (suppress) the secretion of both TRH and TSH.

TRH, TSH pathway
TSH binds to the TSH receptor on the thyroid cells → formation of cyclic AMP (cAMP)-mediated synthesis and release of thyroid hormones (T3 and T4).

T3, T4 pathway
T_3, T_4 in circulation interact with the thyroid hormone receptor (TR) → form a hormone-receptor complex that translocates to the nucleus → initiating transcription.

1- Hypothyroidism:

- Hypothyroidism: decreased levels of thyroid hormones in the circulation.
- Caused by **structural** and **functional derangement**
- **Prevalence** of overt hypothyroidism is **0.3% (**which had been documented); while the **subclinical** is greater than 4% (not diagnosed cases).
- High incidence in: **female** by ten folds, increase with **old age**.
- Classified as :

	Primary (abnormal thyroid)	**Secondary** (abnormal hypothalamus or pituitary)
Cretinism: infancy (usually congenital)	1/ *developmental* (thyroid dysgenesis: *PAX8, FOXE1*, TSH receptor mutations) 2/ *Congenital biosynthetic defect* by - *Endemic iodine deficiency* (most common) -Inborn errors (dyshormonogenetic goiter)	*Pituitary failure* *Hypothalamic failure* Both are extremely rare
Myxedema: older child - adult - elderly (usually acquired or could be familial)	1/ *surgical, radioiodine, external irradiation* 2/ *Autoimmune* **(Hashimoto 80%-90%)** most common in iodine sufficient area.	

Cretinism: severe mental retardation, short stature, coarse facial features, a protruding tongue, and umbilical hernia.
Glycosaminoglycans and hyaluronic acid deposition (with unknown cause), in skin, subcutaneous tissue, visceral sites → myxedema.

Myxedema: slowing of physical and mental activity, mental sluggishness-overweight.

Other hypothyroidism features are Non-pitting edema, a broadening and coarsening of facial features, enlargement of the tongue, deepening of the voice.

> ***REMEMBER:***
> Hypothyroidism is caused by both very high and low iodine intake.
>
> Hypothyroidism will cause mental and physical retardation.

2- Hyperthyroidism:

- **Hypermetabolic state** caused by elevated circulating levels of **free T3 and T4.**
- Caused most commonly by hyperfunction of the thyroid gland.
- The common practice is to use the terms **thyrotoxicosis** (increase the amount of thyroid hormone whatever the cause and hyperthyroidism is the major cause of it) or **hyperthyroidism** (hyper activity of thyroid gland).

Causes of Thyrotoxicosis (associated with hyperthyroidism):

- Primary
  1- Diffuse hyperplasia of the thyroid associated with **Graves' disease** (**accounts for 85% of cases**)
  2- Hyperfunctional multinodular goiter (most of cases are associated with normal thyroid hormone).
  3- Hyperfunctional adenoma of the thyroid (most of cases the nodules are nonfunctional or **cold nodules**)
- Secondary:
  1- TSH-secreting pituitary adenoma (rare)

Causes of Thyrotoxicosis (mostly temporary) (May not be associated with hyperthyroidism):

1- Granulomatous (de Quervain) thyroiditis (painful)
2- Sub acute lymphocytic thyroiditis (painless)
3- Struma ovarii (ovarian teratoma with ectopic thyroid)
4- Factitious thyrotoxicosis (exogenous thyroxin intake)→**common with people in medical field**

Specialized teratoma: a rare subtype of teratoma is composed entirely of specialized tissue. The most common example is *struma ovarii*, which is composed entirely of mature thyroid. That actually secret thyroid hormone.

Graves' disease

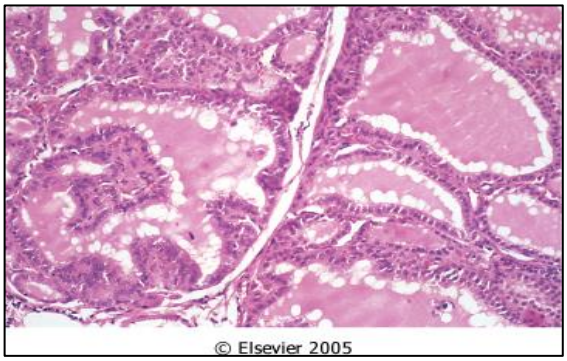
- Graves: 1835: "violent and long continued palpitations in females" associated with enlargement of the thyroid gland.
- Graves' disease is an ***autoimmune disorder*** (autoantibodies to the TSH receptor are central to disease pathogenesis):
- LATS (long acting thyroid stimulating) IgG antibody : anti-TSH receptor
- Coexistence of stimulating and inhibiting immunoglobulins in the serum of the same patient, a finding that could explain why some patients with Graves' disease spontaneously develop episodes of hypothyroidism.

Clinical features:

- Hyperthyroidism owing to hyper-functional, diffuse bilateral enlargement.
- Infiltrative ophthalmopathy (exophthalmos).
- Localized, infiltrative dermopathy (pretibial myxedema).

Microscopic features:

- Hyperplasia of thyroid gland
- Enlarged irregular lymphoid follicles
- Enlarged epithelial cells project into the lumens of the follicles.
- Pseudo-papillary like formation (due to hyper activity of the gland)



3- Thyroditis:

Thyroiditis, or inflammation of the thyroid gland encompasses a diverse group of disorders characterized by some form of thyroid inflammation. These diseases include conditions that result in:

1- **Acute illness** with severe **thyroid pain** (e.g., infectious thyroiditis, sub-acute granulomatous thyroiditis).
2- Disorders in which there is relatively **little inflammation** and the illness is manifested primarily by thyroid dysfunction (subacute lymphocytic thyroiditis and fibrous [Reidel] thyroiditis).

From Robbins:

Other types of thyroiditis:
Sub-acute lymphocytic: painless or silent, most likely to be autoimmune in etiology.
Riedel thyroiditis: unknown etiology, extensive fibrosis extend beyond the capsule of the gland (unlike Hashimoto fibrosis), hard and fixed thyroid mass.

Note: Thyroiditis includes two stages:
Short → thyrotoxicosis (very high Thyroid hormones in circulation) caused by disruption of the cells → ruptured cells will release their content in the circulation → elevated free T3 & T4, low TSH (primary hyperthyroidism)

Long → After inflammation, cells are distracted so no new formation of T3 & T4 → T3 & T4 level decrease progressively (Hypothyroidism), high TSH.

Many diseases are associated with thyroiditis:

1-Hashimoto thyroiditis (Struma lymphomatosa):

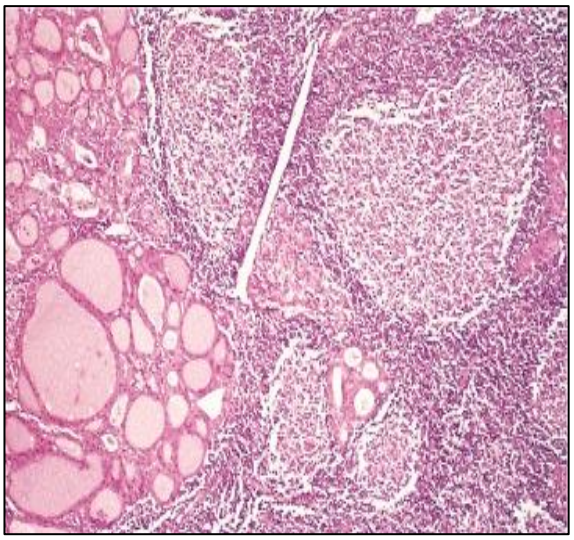
- Chronic lymphocytic thyroiditis.
- Diffuse bilateral enlargement of thyroid gland (like in Graves' disease).
- The most common cause of hypothyroidism in iodine sufficient areas.
- Autoimmune disorder causes gradual destruction of thyroid gland
- Female predominance of 10:1 to 20:1. Age 45-65.

Pathogenesis	Clinically
Hashimoto thyroiditis is an autoimmune disease in which the immune system reacts against a variety of thyroid antigens (thyroglobulin and thyroid peroxidase). The feature of Hashimoto's thyroiditis is progressive depletion of thyroid epithelial cells (thyrocytes), replaced by mononuclear cell infiltration and fibrosis. High susceptibility to Hashimoto is associated with polymorphism in multiple immune-regulation genes: CTLA4 is the most significant.	- **Painless** *enlargement* of the thyroid, usually associated with the degree of **hypothyroidism** develops gradually. - The enlargement is usually *symmetric and diffuse*. Patients with Hashimoto often have other autoimmune disease, and a high risk for developing B cell non-Hodgkin lymphoma.

Morphology:

Macroscopic:

- The cut surface is pale and gray tan in appearance, the tissue firm and friable.



Microscopic:

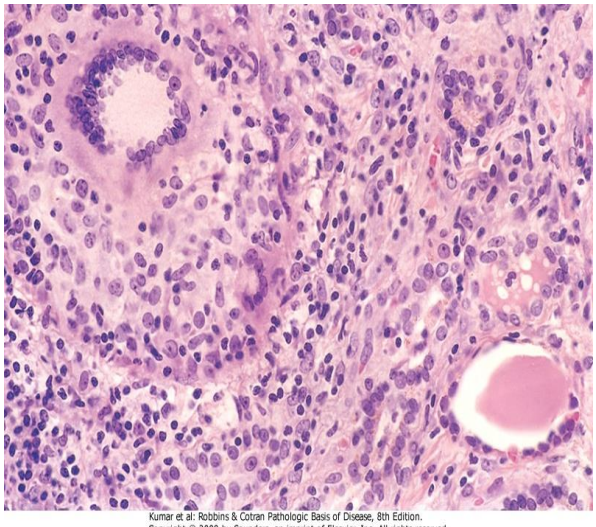
1/ examination reveals *extensive infiltration* of the parenchyma by a mononuclear inflammatory infiltrate containing small ***lymphocytes***, ***plasma cells***, and well-developed ***germinal centers***

2/ The thyroid follicles are ***atrophic*** (fibrosis) and are lined in many areas by epithelial cells distinguished by the presence of abundant ***eosinophilic***, ***granular cytoplasm***, numerous mitochondria termed **Hürthle cells**.

REMEMBER:
Hashimoto thyroiditis and Graves's disease are the two most common immunologically mediated disorders of the thyroid

2-Sub-acute granulomatous thyroiditis (de Quervain)

- Caused by *Viral Infection* or inflammatory Process triggered by virus e.g., (coxsackie virus, mumps.)
- By contrast, with autoimmune, it is *self-limiting*.
- Usually affect females around the age of 60



Morphology:

- Granulomatous inflammation with giant cells.

Clinical findings:

- Less common
- History of upper *respiratory infection*.
- Painful thyroid
- Initial thyrotoxicosis from gland destruction

(As long as it is a self-limiting disease, it will only show the first temporary of thyroiditis: hyperthyroidism)

Note: Hashimoto and Graves both are autoimmune diseases but,
Hashimoto: causes thyroiditis, autoimmune antibodies cause damage to the cell
Graves: autoimmune antibodies are only mimicking the action of TSH, by activating TSH receptors without causing cell destruction.

Summary (from Robbins Basic Pathology):

Chronic lymphocytic (Hashimoto) thyroiditis is the most common cause of hypothyroidism in regions where dietary iodine levels are sufficient.
Hashimoto thyroiditis is an autoimmune disease characterized by progressive destruction of thyroid parenchyma, Hürthle cell change, and mononuclear (lymphoplasmacytic) infiltrates, with or without extensive fibrosis.
Multiple autoimmune mechanisms account for Hashimoto disease, including cytotoxicity mediated by CD8+ T cells, cytokines (IFN-γ), and antithyroid antibodies.
Subacute granulomatous (de Quervain) thyroiditis is a self-limited disease, probably secondary to a viral infection, and is characterized by pain and the presence of a granulomatous inflammation in the thyroid.
Subacute lymphocytic thyroiditis is a self-limited disease that often occurs after a pregnancy (postpartum thyroiditis), typically is painless, and is characterized by lymphocytic inflammation in the thyroid.
Graves' disease, the most common cause of endogenous hyperthyroidism, is characterized by the triad of thyrotoxicosis, ophthalmopathy, and dermopathy.
Graves' disease is an autoimmune disorder caused by autoantibodies to the TSH receptor that mimic TSH action and activate TSH receptors on thyroid epithelial cells.
• The thyroid in Graves' disease is characterized by diffuse hypertrophy and hyperplasia of follicles and lymphoid
infiltrates; glycosaminoglycan deposition and lymphoid infiltrates are responsible for the ophthalmopathy and
dermopathy.
• Laboratory features include elevations in serum free T3 and T4 and decreased serum TSH.

	Hypothyroidism	Hyperthyroidism
Causes	- **Primary :** in the gland itself Developmental , Postablative, Iodine deficiency, surgery , Autoimmune hypothyroidism Hashimoto thyroiditis. - **Secondary (central):** Pituitary failure, Hypothalamic failure.	***ASSOCIATED WITH HYPERTHYROIDISM:*** **Primary:** 1- Diffuse hyperplasia of the thyroid associated with Graves' disease (accounts for 85% of cases). 2- Hyperfunctional multinodular goiter. 3- Hyperfunctional adenoma of the thyroid. **Secondary:** TSH-secreting pituitary adenoma. ***NOT be associated with hyperthyroidisim:*** ▪ Granulomatous (de Quervain) thyroiditis. ▪ Subacute lymphocytic thyroiditis. ▪ Struma ovarii . ▪ Factitious thyrotoxicos.
Example	Hashimoto's Thyroiditis	Graves' disease
	Autoimmune disease	
Mechanism of the disease	The immune system reacts against a variety of thyroid antigens (thyroglobulin and thyroid peroxidase).	Autoantibodies to the TSH receptor.
Clinical findings And features	▪ Lymphocytic infiltration with plasma cells. ▪ Transformation of the epithelium to larger cells with larger nuclei and granular cytoplasm (Hürthle cells).	▪ Hyperfunctional, diffuse enlargement. ▪ Exophthalmos. ▪ Localized, infiltrative dermopathy (pretibial myxedema).

Questions

1/ A 46-year-old woman complains of increasing fatigue and muscle weakness over the past 6 months. She reports an inability to concentrate at work and speaks with a husky voice. The patient denies drug or alcohol abuse. Physical examination reveals cold and clammy skin, coarse and brittle hair, boggy face with puffy eyelids, and peripheral edema. There is no evidence of goiter or exophthalmos. Laboratory studies show reduced serum levels of T3 and T4. Which of the following is the most likely under- lying cause of these signs and symptoms?

(A) Amyloidosis of the thyroid
(B) Hypothyroidism
(C) Thyroid follicular adenoma
(D) Multinodular goiter

2/ A 40-year-old woman complains of chronic constipation and anovulatory cycles for the last 8 months. Her vital signs are normal. Physical examination reveals peripheral edema and a firm, diffusely enlarged thyroid gland. Serum levels of T3 and T4 are abnormally low. A thyroid biopsy is shown in the image. What is the appropriate diagnosis?

(A) Acute necrotizing thyroiditis
(B) Hashimoto's thyroiditis
(C) Multinodulargoiter
(D) Subacute (DeQuervain) thyroiditis

3/ A 43-year-old woman complains of low-grade fever and has a 3-day history of pain in her neck. Physical examinarions reveals a slightly enlarged thyroid. A CBC is normal. A biopsy of the thyroid reveals granulomatous inflammation and the presence of giant cells. What is the appropriate diagnosis?

(A) Gravesdisease
(B) Hashimotothyroiditis
(C) Lymphadenoidthyroiditis
(D) Subacute (deQuervain) thyroiditis

4/ Patient has symptoms of hyperthyroidism. Which of the following best summarizes the clinical symptoms expected in this patient?

(A) Dry skin, hypogonadism, fatigability
(B) Hyperpigmentation, weakness, hypotension
(C) Nervousness, irritability, paresthesias, tetany
(D) Tremor, tachycardia, weight loss

Answers:

- 1- B
- 2- B
- 3- D
- 4- D

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com

432 Pathology Team Leaders:
Roqaih Al-Dueb & Ibrahim Abunohaiah

*Good Luck ^_^*