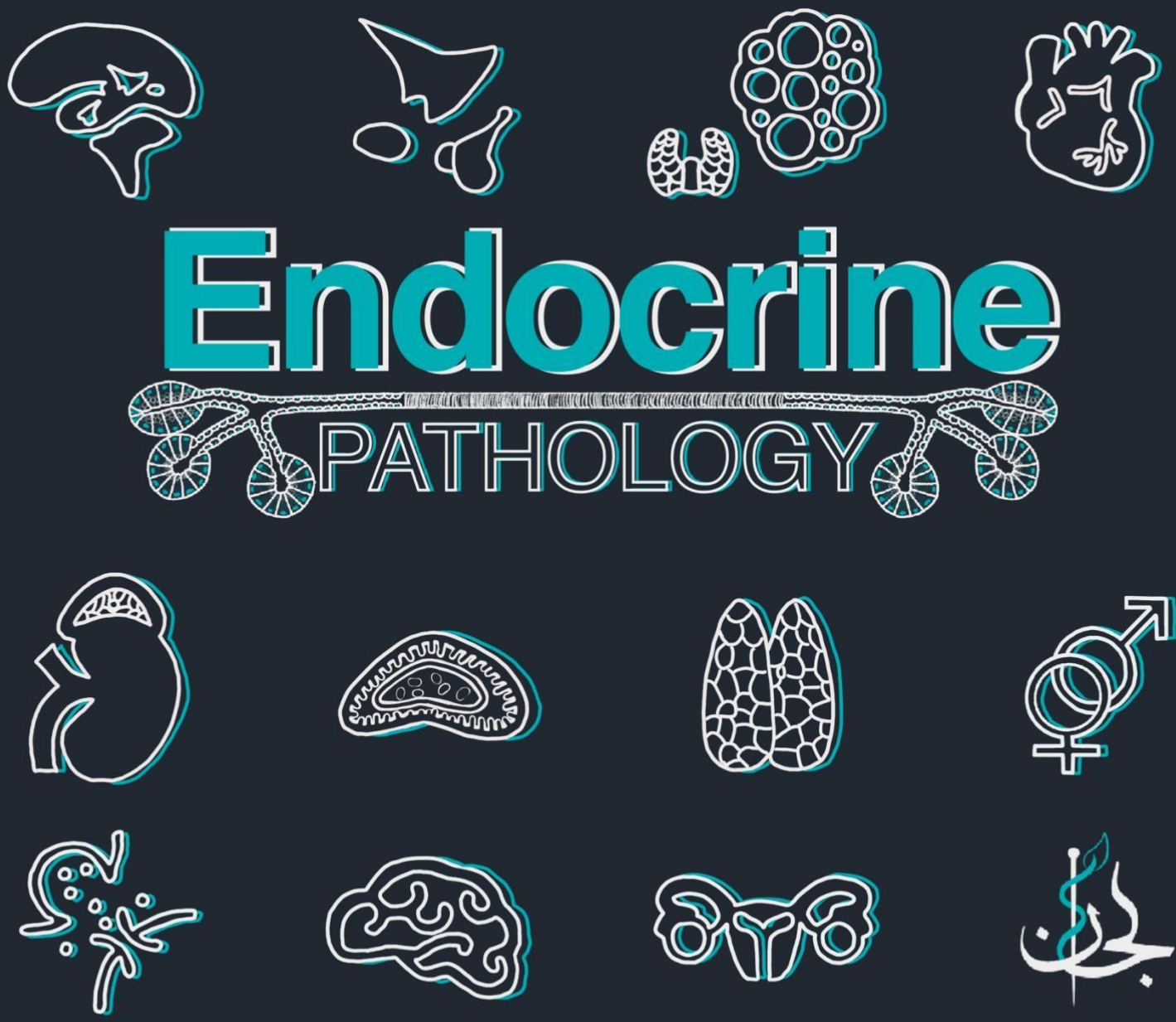

Endocrine PATHOLOGY

Title: Sheet 3 – Diseases of the Thyroid Gland

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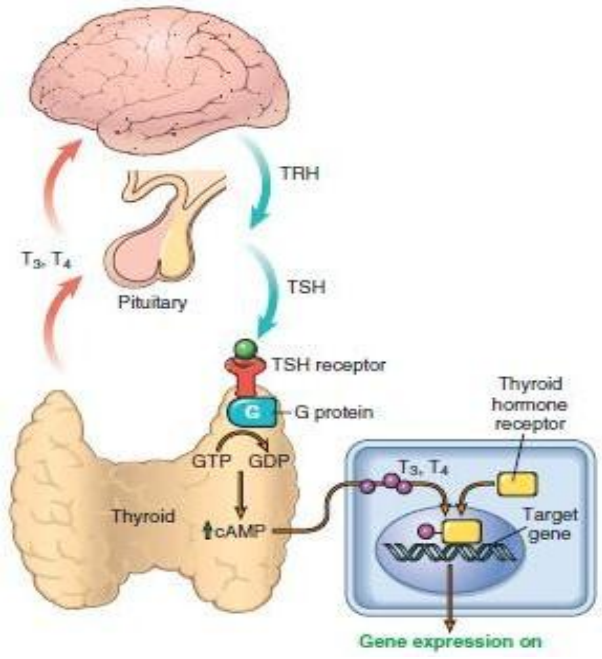
In this lecture, we will start talking about Thyroid gland pathology.

A quick revision of the anatomy and physiology of the thyroid gland. (from Robbins, you can skip it)

- The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx. The thyroid is divided into lobules, each composed of dispersed follicles. The follicles are lined by epithelium, which is filled with thyroglobulin, the iodinated precursor protein of active thyroid hormone.
- In response to trophic factors (TRH) from the hypothalamus, TSH (also called *thyrotropin*) is released by thyrotrophs in the anterior pituitary into the circulation.
- The binding of TSH to its receptor on thyroid follicular epithelial cells results in activation and conformational change in the receptor, allowing it to associate with a stimulatory G-protein. Activation of stimulatory G-protein results in an increase in intracellular cAMP levels, which stimulates thyroid hormone synthesis and release.



- Thyroid follicular epithelial cells convert thyroglobulin into *thyroxine* (T4) and lesser amounts of *triiodothyronine* (T3). T4 and T3 are released into the systemic circulation, where most of these peptides are bound to circulating plasma proteins, such as T4-binding globulin, for transport to peripheral tissues. The binding proteins maintain the serum unbound (free) T3 and T4 concentrations within narrow limits while ensuring that the hormones are readily available to the tissues.
- In the periphery, the majority of free T4 is deiodinated to T3; the latter binds to thyroid hormone nuclear receptors in target cells with 10-fold greater affinity than T4 and has proportionately greater activity. Binding of thyroid hormone to its nuclear thyroid hormone receptor (TR) creates a hormone-receptor complex that regulates the transcription of a subset of cellular genes. This produces diverse cellular effects, **including increased carbohydrate and lipid catabolism** and **protein synthesis** in a wide range of cell types. The net result of these processes is an ***increase in the basal metabolic rate***.

Clinical recognition of diseases of the thyroid is important, because most are amenable to medical or surgical management. Such diseases include conditions associated with:

- excessive release of thyroid hormones (hyperthyroidism), thyroid hormone deficiency (hypothyroidism), and mass lesions of the thyroid.

I. Thyrotoxicosis

- Thyrotoxicosis refers to *increased circulating thyroid hormone*, regardless of the cause of the increase.
- Hyperthyroidism, *which is the most common cause of Thyrotoxicosis*, means increased thyroid hormone **production** and **secretion** from the thyroid gland. (An actual increase in Thyroid hormone **PRODUCTION**)

NOTE: In the case of **Thyroiditis** "*inflammation of thyroid gland,*" there is destruction of the thyroid gland. This causes increased **release** of thyroid hormones (there is a relative net increase in T3 & T4) without increased production. So, we have *Thyrotoxicosis **without** Hyperthyroidism*. (Not an actual increase, because there is no increase in production).

A. *Thyrotoxicosis Associated with Hyperthyroidism (Thyroid Hyperfunction)*:

1. *Primary*: When the disease directly affects the thyroid gland:

A. Diffuse Toxic Hyperplasia/Goiter (***Graves disease***): Occurs when autoantibodies attack the thyroid gland, causing it to produce more T3 and T4. (Extra: These autoantibodies have an action similar to TSH, they DON'T destroy TSH receptors as you might think).

B. Hyperfunctioning (Toxic) Multinodular Goiter: Goiter means an enlarged thyroid gland. Multinodular goiters typically are hormonally silent (euthyroid=no change in hormones levels=non-toxic), but 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 is known as *toxic multinodular goiter*.

C. Hyperfunctioning (Toxic) Follicular Adenoma: Usually euthyroid, but in rare cases, when an excess amount of thyroid hormone is produced, it is toxic.

2. *Secondary*: **TSH**-Secreting Pituitary Adenoma (rare): Adenoma in the anterior pituitary that secretes **TSH**.
Remember that **TSH** is secreted from the *Anterior Pituitary* to stimulate production of **T3** and **T4**.

B. *Thyrotoxicosis not associated with hyperthyroidism*: (less common)
- Excessive *release* of pre-formed hormones in thyroiditis.
(just increased release with no increased overall production)

Functions of thyroid hormones:

-They increase basal metabolic rate, increase breakdown of fat and glucose and increase appetite despite weight loss.
-They increase heart rate, causing hypertension.
-They increase sweating and body temperature.
- They co- regulate long bone formation with growth hormone.
- They play a role in neural maturation.

So, with any increase or decrease in their levels, we expect to see a wide range of *clinical manifestations*.

Clinical Manifestations of Thyrotoxicosis (Important)

A. Constitutional symptoms: warm flushed skin, heat intolerance and excessive sweating, weight loss despite increased appetite.

B. Malabsorption and diarrhea (because of increased intestinal motility).

C. Tachycardia and elderly patients may develop heart failure due to aggravation of pre-existing heart disease.

D. Nervousness, tremor (حركات ال ارادية) , and irritability.

E. A wide, staring gaze and lid lag (your upper eyelid is higher than normal while you are looking down) because of sympathetic overstimulation of the levator palpebrae superioris.

F. 50% develop proximal muscle weakness (thyroid myopathy), a neuromuscular disorder that leads to muscle weakness and muscle tissue breakdown.

Lab tests:

• The measurement of serum **TSH** is the single most useful screening test for hyperthyroidism, because **TSH** levels are decreased even at the earliest stages, when the disease may still be subclinical.

Note: As a result of the high concentration of thyroid hormones, negative feedback inhibits production of TSH.

Once the diagnosis of thyrotoxicosis has been confirmed, measurement of Radioactive Iodine Uptake by the thyroid gland is valuable in determining the **etiology**.

For example, such scans may show:

A. If there's diffuse uptake of iodine by the whole gland, the disorder is most likely ***Graves Disease.***

B. Increased uptake in a solitary nodule is seen in *toxic follicular adenoma* or a *toxic nodule of the multinodular goiter.*

C. When there is a decrease in uptake of iodine, it's most likely *Thyroiditis*.

Recall: Iodine is needed for the conversion of tyrosine into Monoiodotyrosine **(MIT)** and Diiodotyrosine **(DIT).**

DIT + DIT give **T4**

MIT + DIT give **T3**

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II. HYPOTHYROIDISM

This disorder may be divided into:

A- Primary hypothyroidism, which is due to an intrinsic abnormality in the thyroid gland and can be classified as:

1. Congenital: A genetic defect that interferes with thyroid development and we call this (Thyroid dysgenesis). Or, a genetic defect that interferes with the synthesis of thyroid hormone and we call this (Dyshormonogenetic goiter).

Congenital causes are rare overall.

2. Endemic deficiency of dietary Iodine is typically manifested by Hypothyroidism early in childhood and has also been considered congenital

– It is a common cause of Hypothyroidism in infants and children worldwide

3. Autoimmune Thyroid Disease is a common cause of hypothyroidism in regions of the world where iodine is supplemented in dietary salt products (iodine in the diet is sufficient).

-*The vast majority of cases of autoimmune hypothyroidism is due to* **Hashimoto thyroiditis**

4. Iatrogenic Hypothyroidism can be caused by surgical or radiation-induced **ablation** of thyroid parenchyma, or as an adverse effect of certain drugs.

B- Secondary Hypothyroidism: Arises from an abnormality of the hypothalamus or pituitary.

The clinical manifestations of hypothyroidism include cretinism$_1$ and myxedema$_2$

1. Cretinism:
    - Occurs in infants and children and can be either:

A. *Endemic cretinism*: caused by iodine deficiency. It is now less frequent due to supplementation of salt with iodine.

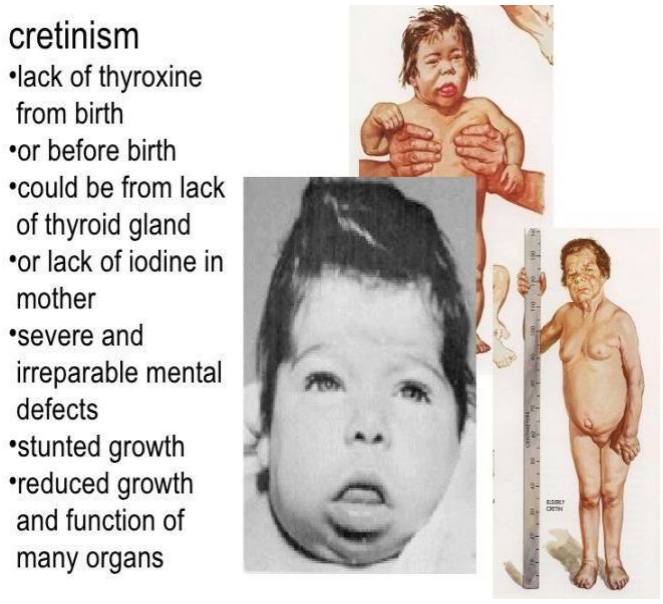
B. *Sporadic* due to an enzyme that interferes with thyroid hormone synthesis.

Clinical Features of Cretinism

A. Impaired development of the skeletal system.

B. Impaired development of central nervous system which manifests as:

- Severe mental retardation. Remember that the thyroid is important for brain development.
- Short stature, قصر القامة" "coarse facial features, a protruding tongue, and umbilical hernia.



2.Myxedema

- Hypothyroidism in older children and adults
- The initial symptoms include generalized fatigue, apathy, and mental sluggishness.
- *Decreased sympathetic activity results in constipation and decreased sweating*.
- The skin is cool and pale because of decreased blood flow.
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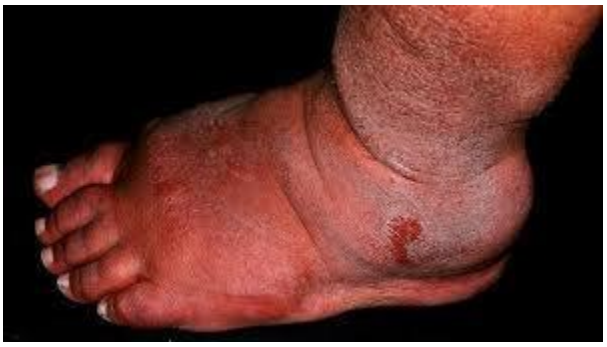

EXTRA: Myxedema is the accumulation of glycosaminoglycans in the skin and soft tissue. So, it is not a true edema (collection of fluid), it is MYXedema.

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III. Thyroiditis

1.Chronic Lymphocytic (Hashimoto) Thyroiditis:

Hashimoto (a Japanese scientist who discovered it) **thyroiditis** is the most common cause of hypothyroidism in areas of the world where iodine is supplemented in dietary salt.

- It is characterized by gradual thyroid failure secondary to ***autoimmune destruction of the thyroid gland***.
- It is most prevalent in individuals between 45 and 65 years of age and is more common in females.
- Although it is primarily a disease of old women, it can occur at any age, including childhood.

MORPHOLOGY:

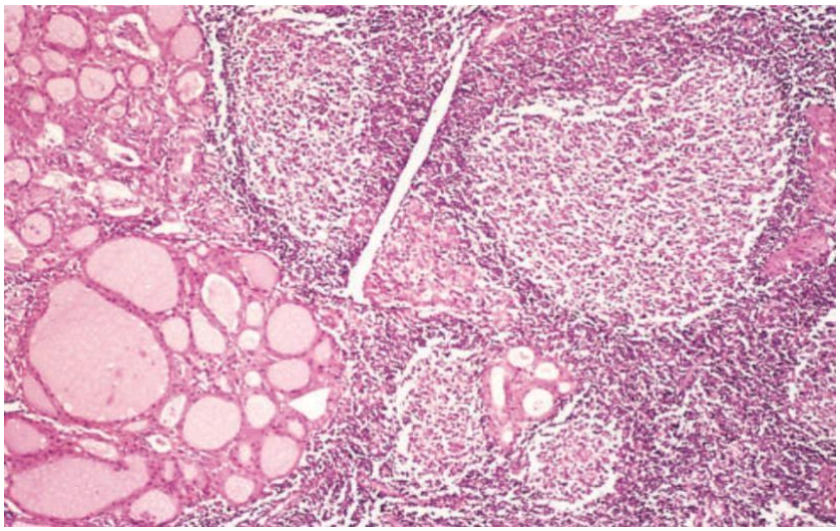
- The thyroid is usually diffusely and **symmetrically** enlarged (both lobes are involved).
- Microscopic examination reveals widespread infiltration of the parenchyma by a mononuclear inflammatory infiltrate containing small lymphocytes, plasma cells, and well-developed germinal centers.

The *germinal center* is the site of maturation of lymphocytes.

- The thyroid follicles are **atrophic** and lined by epithelial cells, distinguished by the presence of abundant, ***eosinophilic***, granular cytoplasm, termed **Hürthle**, or **Oxyphil** cells.
- Normally, follicles are lined by epithelial cells. Chronic inflammation causes metaplasia of these epithelial cells into **Hürthle** cells.

Histopathology of Hashimoto Thyroiditis

- To the left there are many follicles that contain colloid in their lumen lined by **Hürthle** cells. While to the right we notice the appearance of a germinal center that is pale in color and surrounded by lymphocytes (bluish area).



Clinical Manifestations

Painless enlargement of the thyroid usually associated with some degree of hypothyroidism.

- The enlargement of the gland usually is *symmetric and diffuse as we said*.
- In the usual clinical course, hypothyroidism develops gradually.
- In some cases, Patients initially present with thyrotoxicosis (**Hashitoxicosis**) due to destruction of thyroid follicles by inflammatory cells. During this phase, **T4** and **T3** are elevated, **TSH** is diminished, and iodine uptake is decreased. (when the follicles are destroyed they release the pre-formed hormones).

- **Then**, in both cases (if there is Hashitoxicosis or not), as the thyroid is being destroyed, the amount of **T3** and **T4** will start to decrease below the normal levels (Hypothyroidism). As Hypothyroidism supervenes, **T4** and **T3** levels progressively fall, accompanied by a compensatory increase in **TSH**.

- Similar to other autoimmune disorders, patients with Hashimoto Thyroiditis often have other autoimmune diseases.
- Patients are at an increased risk for the development of **B-cell non-Hodgkin Lymphomas,** which typically arise within the thyroid gland.

NOTE:

A lymphoma is a malignant tumor of lymphoid tissue, divided into Hodgkin and non-Hodgkin types. They are of either B-cell or T-cell origin. Patients of Hashimoto thyroiditis are at an increased risk to develop **B-cell non-Hodgkin Lymphomas.**

- Molecular and morphological studies suggest that people with Hashimoto Thyroiditis are susceptible to **papillary thyroid carcinoma**.

2. Subacute Granulomatous Thyroiditis, also called (de Quervain)

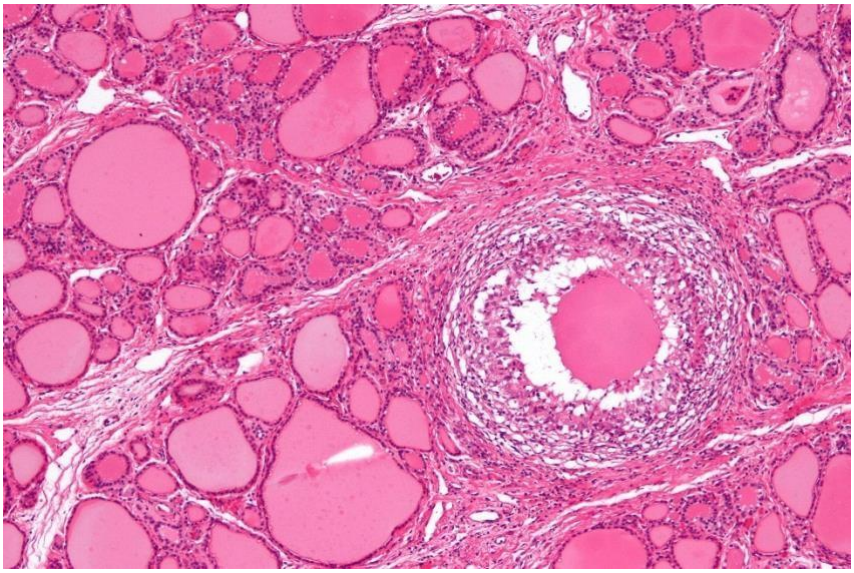
- *Granulomatous thyroiditis that follows viral infection.*
- Rupture of follicles leads to leaking out of colloid (extravasation) that induces granuloma formation.
- It is much less common than Hashimoto disease.
- Is most common in individuals between 30 and 50 years of age, with a higher frequency in females than males.
- *A majority of patients have a history of an upper-respiratory infection shortly before the onset of thyroiditis* (that's why it is believed that it develops in relation to the viral infection).
- The process spontaneously remits. (usually self-limited)

• MORPHOLOGY

- The gland is enlarged symmetrically with the capsule intact.
- Histologic examination reveals infiltrating neutrophils, which are replaced over time by lymphocytes, plasma cells, and macrophages. It also reveals the disruption of thyroid follicles and extravasation of colloid.
- The extravasated colloid initiates an exuberant granulomatous reaction.

Cont…

- In this picture we can see follicles that contain colloid in their lumen (left) and a granuloma (right).
- The granuloma contains epithelioid macrophages, giant cells and some fragments of colloid.
- There is no necrosis in its center, so we call it a non-caseating granuloma.



Clinical Features:

- The onset often is acute. The condition typically is self-limited, with most patients returning to a euthyroid state (normal levels of thyroid hormones) within 6 to 8 weeks.
- It is characterized by neck pain (especially with swallowing). Fever and malaise may also occur, with variable enlargement of the thyroid gland due to the presence of inflammatory cells.
- Transient Thyrotoxicosis (not hyperthyroidism) may occur as a result of disruption of thyroid follicles and release of excessive preformed thyroid hormone. With progression of the gland destruction, a transient hypothyroid phase may ensue. But again, in most patients the disease is self-limited.
- The leukocyte count and erythrocyte sedimentation rates are increased.

3.Subacute Lymphocytic Thyroiditis

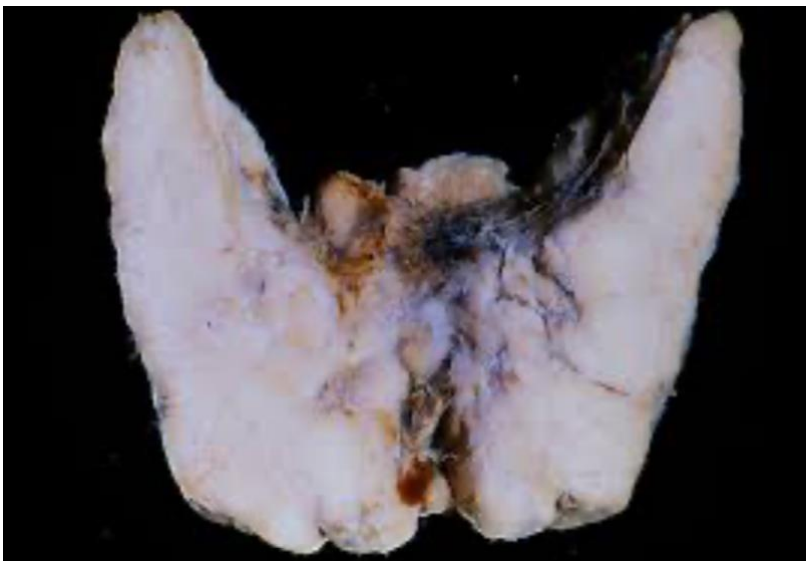
- Also is known as silent or painless thyroiditis.
- In some female patients, the onset follows pregnancy (postpartum thyroiditis).
- This disease is most likely autoimmune in etiology, due to the presence of circulating antithyroid antibodies that are found in a majority of patients.
- The patients present with a painless neck mass and features of thyroid hormone excess.
- The initial phase of thyrotoxicosis is followed by the return to a euthyroid state within a few months.
- In a minority of affected individuals, the condition eventually progresses to **hypothyroidism**.

4. Riedel Thyroiditis:

- Is characterized by **extensive fibrosis** involving the thyroid and adjacent neck structures.
- Clinical examination demonstrates a hard and fixed thyroid mass, simulating a thyroid neoplasm.
- It may be associated with idiopathic fibrosis in other sites in the body, most commonly in the *retroperitoneum*.

- Notice the white appearance of the thyroid gland due to fibrosis.

- Because of the fibrosis, the gland is **HARD** when you touch it and fixed to the structures of the neck. So, physicians may inaccurately diagnose the condition as cancer.



Short Quiz

1- A 37-year-old woman has had difficulty swallowing and a feeling of fullness in the anterior neck for the past week. She is recovering from a mild upper respiratory tract infection 1 month ago. On physical examination, her temperature is 37.4° C, pulse is 74/min, respirations are 16/min, and blood pressure is 122/80 mm Hg. Palpation of her diffusely enlarged thyroid elicits pain. Laboratory studies show an increased serum T4 level and a decreased TSH level. Two months later, she no longer has these complaints. The T4 level is now normal. Which of the following conditions is most likely to have produced these findings?

A) Hashimoto thyroiditis B) Medullary thyroid carcinoma
C) Subacute granulomatous thyroiditis D) Toxic follicular adenoma
E) Toxic multinodular goiter

2- A 30-year-old woman has given birth to her second child. She develops heat intolerance and loses more weight than expected postpartum. On physical examination, her thyroid gland is enlarged but painless; there are no other remarkable findings. Laboratory studies show a serum T4 level of 12 µg/dL and a TSH level of 0.4 mU/L. A year later she is euthyroid. Which of the following is most indicative of the pathogenesis of this patient's disease?

A) Activational mutations in the RET proto-oncogene B) Anti–thyroid peroxidase antibodies C) Irradiation of the neck during childhood
D) Prolonged iodine deficiency E) Recent viral upper respiratory tract infection

3-During a yearlong training program, a 23-year-old female Air Force officer falls in class rank from first place to last place. She has also noted a lower pitch to her voice and coarsening of her hair, along with an increased tendency toward weight gain, menorrhagia, and increasing intolerance to cold. Which of the following laboratory abnormalities is expected?

(a) Increased serum free T4

(b) Increased saturation of thyroid hormone-binding sites on TBG
(c) Increased serum TSH (d) Decreased serum cholesterol

4. A 35-year-old woman presents with amenorrhea and weight loss despite increased appetite. The history and physical examination reveal exophthalmos, fine resting tremor, tachycardia, and warm, moist skin. Laboratory tests for thyroid function would be expected to yield a decreased value for which of the following?

(a) Free T4 (B) Radioactive iodine uptake

(c) T3 (d) Thyroid stimulating hormone

Answers:

1- C

2- B

3- C

4- D