The Endocrine System

PATHOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	2
Subject:	Non-neoplastic thyroid gland diseases
Done By:	Sara Zayadneh
Corrected by:	Mohammad Karajeh
Doctor:	Tareq Adily

Date:	
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Salam ☺

This sheet was written according to the record of section 2. It covers slides (22-38), there is no need to go through the slides as the sheet includes them.

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Non-neoplastic thyroid gland diseases.

[1] – Chronic lymphocytic (Hashimoto) thyroiditis.

A disease was first discovered in Japan.

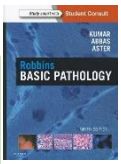
- Most common cause of hypothyroidism.
- Peak incidence → middle age (45-65).
- More common in women, F:M >10 .

When we say "more common in women", we can predict the nature of the disease, which is Autoimmune, unlike all other diseases which are common in men.

Hashimoto thyroiditis is characterized by progressive destruction and depletion of follicular epithelial cells of thyroid gland.

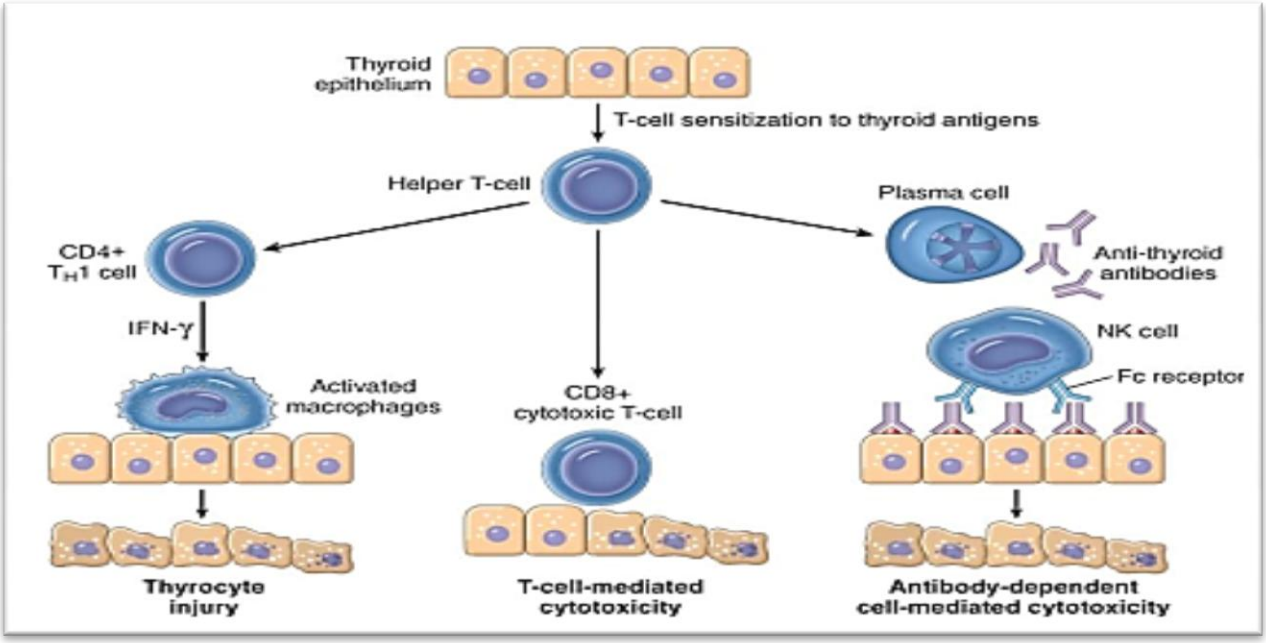
- Always in autoimmune diseases there is an abnormality in CD4 + T-lymphocytes, so they are abnormally functioning and they lose the normal self-recognition.
- They recognize the follicular epithelial cells as something foreign.
- Once they are activated they activate other cells ((**macrophages, NK-cells, plasma cells**)) to cause damage, so they don't do the destruction by themselves.

1) Macrophages :
   Are activated by INF- γ secreted by T-lymphocytes.



From Robbins:

- Cytokine-mediated cell death→ excessive T cell activation leads to production of inflammatory cytokines such as INF- γ in the thyroid gland, with resultant recruitment and activation of macrophages and damage of follicles.



2) NK-cells:

Are indirectly activated by plasma cells, helper T-cells to secrete antibodies against the follicular epithelial cells "Auto-antibodies".

➔ Plasma cells coat the follicular epithelial cells, which cause the activation of NK-cells →we end up with a damage to the follicular cells.

3) CD8+ cytotoxic cell mediated cell death:

CD8+ cytotoxic T cells may cause thyrocyte destruction.

- Genetic predisposition:

  Hashimoto disease is more common in certain cases:

*with family history.

*HLA-DR3.

*HLA-DR5.

These are antigens in the WBCs, normally variant; some people have them, and some other do not have them.

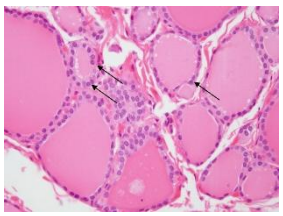
- Grossly → thyroid gland enlargement because of the presence of inflammatory cells, but the enlargement is diffuse "homogeneous".

- Intact capsule, not adherent to near structures, unlike cancer, which is invasive.

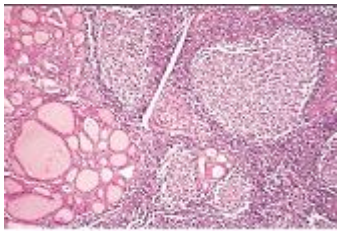
For description of thyroid gland enlargement clinically we use the term GOITER→a large thyroid in normal people, except in pregnancy, so we cannot feel thyroid gland in normal people except pregnancy.

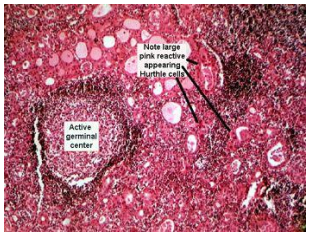
- Under microscope:
  We have many inflammatory cells (dense infiltration of lymphocytes), B-lymphocytes forming germinal centers, plasma cells, T-lymphocytes and macrophages.
- Follicular epithelium:

Normal histology→cuboidal, single cell-like in each follicle.



In Hashimoto,→follicular epithelium is atrophic, show metaplastic changes into large, pink cuboidal cells called **Hurthe** cells or oxyfil cells (similar to those in the stomach) (full of mitochondria).





- With time:
  →Fibrosis; because always inflammation is followed by fibrosis.
  →Atrophy; so the patient will have hypothyroidism.

Recall metaplasia:

Is a shift in morphology from one cell type to another cell type (both of them are normal), secondary to stress.

Clinically

- Painless goiter.
- Initial transient phase of thyrotoxicosis as a result of follicular epithelial cells damage. (colloid leaks out into the blood), then hypothyroidism will be predominant.
- Other autoimmune diseases are common.
- Risk of B-cell lymphomas but not thyroid carcinomas; because of persistent and intensely activated lymphocytes.

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[2] – Subacute Granulomatous (de Quervain) Thyroiditis.

- Most common 30-50.
- Most common in women.
- Viral infection or post viral inflammation (history of upper respiratory tract infection).
- Self-limited, not progressive.

This name is somehow misleading, as granuloma usually occurs in TB and sarcoidosis, in this situation we don't have neither TB nor sarcoidosis, but it is secondary to viral infection.
→we have direct damage by virus "any virus that causes upper respiratory tract infection", sometimes only small antigens from the virus is seeding in the thyroid, causing activation of immune system.

Diagnosis

1. Mostly clinical history, painful goiter not adherent "i.e. something inflammatory", with previously upper respiratory tract infection. al
2. Granuloma under the microscope.

Morphology and clinical

- Under microscope:
  Disruption of thyroid follicles, because of inflammation.
  →Any inflammation in the body starts with neutrophils, granulocytes, and then they are followed by chronic inflammatory cells, which are lymphocytes, plasma cells and macrophages.
- Granuloma:
  Is secondary to colloid, normally the colloid is confined in the follicles, when there is a disruption, the colloid will go out in large quantities, so act as foreign bodies, forming granulomas, followed by inflammation.
- Other signs:
  Fever, malaise, swelling, transient hyperthyroidism, leukocytosis, thyrotoxicosis.

^^

[3]- Subacute Lymphocytic Thyroiditis.

- Silent, painless.
- No or minimal goiter.

*why is it occur?

Unknown, it is thought to be autoimmune.

- Sometimes develop in post-partum women, initial thyrotoxicosis then euthyroid, self-limited, but can return in the next pregnancy.
- Under the microscope:
  →Lymphocytic inflammation, germinal centers (like Hshimoto), but no Hurthle cells (no metaplasia).

[4]- Riedel Thyroiditis.

- Fibrosing disease "not inflammatory", the thyroid gland is totally replaced by collagen fibers.
- Unknown etiology, thought to be autoimmune, because we have minor remnant of inflammatory cells.
- Hard mass, adherent t near structures like invasive carcinoma.
- Associated with fibrosis in other organs "retroperitoneal", ex: kidney, pancreas, great vessels.
- Under microscope:
  Very thick collagen bundles, minimal inflammation and follicles.

Riedel thyroiditis is a rare disease, but it is important because it mimics cancer.

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[5]- Palpation thyroiditis. ⇒ Pathologically not clinically important.

- ✓ Vigorous clinical palpation of thyroid gland "physical trauma".
- ✓ Result in multifocal follicular disruption associated with chronic inflammatory cells and occasional giant-cell formation.
- ✓ Incidentally found:→the patient is normally and does not have hyperthyroidism, if you make a blood test to the thyroxin it is normal.

HOW is palpation thyroiditis diagnosed?

Only under the microscope, we see granuloma, some components of inflammatory cells with giant cell formation.

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[6]- Grave's disease.

- Most common cause of hyperthyroidism.
- Autoimmune disease.
- TRIAD: patients have thyrotoxicosis, ophthalmopathy "most prominent in Grave's", and sometimes they have localized infiltrative dermatopathy called: pretibial myxedema, occurs in dorsal aspect of tibia.

Distinguish:

*Myxedema "from the first lecture",
*Pretibial myxedema.

- Middle age people (20-40), more common in women (F:M 7).
- Genetic predisposition:
  -family history.
  -HLA-DR3 and B8.
  -other autoimmune diseases.
- Transient episodes of hypothyroidism (discussed more in pathogenesis part).

PATHOGENESIS

→Break in CD4 tolerance against normal thyroid antigens (i.e. there is an abnormality in the function of CD4 cells; they become activated upon exposure to follicular epithelial cells).
→Activates B-lymphocytes to secrete autoantibodies. "Similar to antibodies in Hashimoto thyroiditis", these autoantibodies activate the follicular cells proliferation.

1)) **thyroid-stimulating immunoglobulin TSI**, autoantibody that bind TSH receptor and mimics the action of TSH, stimulating adenylyl cyclase, result in secretion of thyroid hormones "specific".
The patient will end up with high number of TSI, which activate follicular epithelial cells.

Note 1 TSI is specific for Grave's disease, if the patient has TSI → Grave's.

2)) **thyroid-growth stimulating immunoglobulin TGI**, another antibody against TSH receptor, stimulates proliferation of follicular epithelial cells. "TGI is less specific than TGS".

Note 2:

TSI→activates the function.

TGI→activates the proliferation.

3)) **TSH-binding inhibitor immunoglobulin TBII**, prevents TSH from normal binding to its receptors and by itself, it binds and stimulates proliferation of follicular epithelial cells, other forms inhibit thyroid function (coexist).

4)) **anti thyroglobulin, anti-thyroid peroxidase Abs** (not specific), sometime appear, sometime they don't.

** The last two mechanisms are the least important ones.

? Why patients are develop ophthalmopathy and dermatopathy?
→normally the soft tissues in the retro-orbital area and in the skin, they contain few amount of TSH receptors. TSH will activate these cells to proliferate.

- Increased size of extra orbital muscles and retro orbital soft tissue causing exophthalmos by:

  • (1) infiltration by inflammatory cells
  • (2) Inflammatory edema
  • (3) Accumulation of extracellular matrix
    (Hyaluronic acid and chondroitin sulfate)
  • (4) increased fat cells.

The two main proteins that are synthesized by fibroblast, either in the orbit or in the skin.

• Exophthalmos is persistent even post treatment.
To treat Grave's disease, they give the patients radioactive iodine. → the iodine is only stored in the thyroid, so the injected iodine will reach the thyroid gland and bind to its cells, because of this binding, the radiation will kill the follicular cells.

So, we intended to destroy the thyroid gland in order to teat Grave's disease, "after that the patient must take thyroxin". The radioactive iodine cannot reach the soft tissues, and this explain why the exophthalmos is persistent even post treatment.

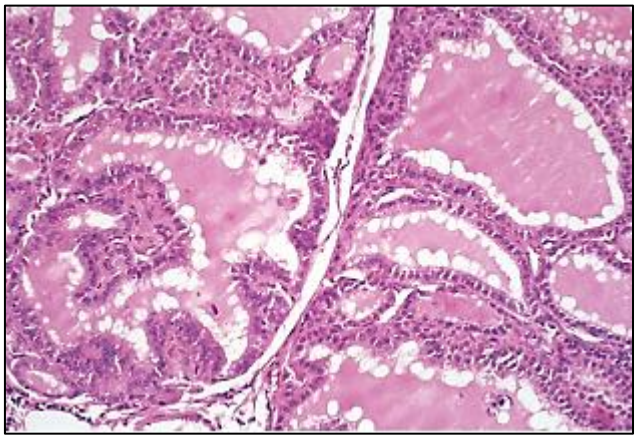
Morphology

→Diffuse goiter, soft, no adherent, intact capsule.
→Under the microscope:

- Follicular epithelial cells are hyperplastic (tall columnar, crowded, small papillae as the cells project into the follicular lumen, and these papillae do not contain fibrovascular core "no vessels", so they aren't true papillae.

*** True papillae is formed from epithelial cells that contain blood vessels inside.

- The colloid is:
-pale; because most of it goes to the blood.
-scalloped margins→ round, irregular, empty spaces like the oyster.



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G☺☺D luck.

Sorry for any mistake.

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