PATHOLOGY OF THE THYROID

T. Utoro
Department of Pathology
Gadjah Mada University School of Medicine
• **Normally** weighs between 20 and 30 g.
• **Follicle** is the functional unit of the thyroid → composed of an epithelium-lined sac filled with colloid → stores thyroid hormones in the form of thyroglobulin → T4 (thyroxine) and T3 (triiodothyronine) → regulated by TSH
• **Serum** T4 and T3 are bound to thyroid-binding globulin (TBG)
Homeostasis in the hypothalamus-pituitary-thyroid axis, and mechanism of action of thyroid hormones.

Cellular effects of thyroid hormones:
- Up-regulation of carbohydrate and lipid catabolism
- Stimulation of protein synthesis in wide range of cells

Net result: Increased the basal metabolic rate.
Pathology of the thyroid

A. CONGENITAL ANOMALY
B. GOITER
C. HYPOTHYROIDISM
D. HYPERTHYROIDISM
E. THYROIDITIS
F. BENIGN TUMORS (ADENOMAS)
G. MALIGNANT TUMORS
Pathology of thyroid

A. CONGENITAL ANOMALY

1. Thyroglossal duct cyst
   - is a remnant of the thyroglossal duct
   - is the most common thyroid anomaly
   - does not lead to alterations in thyroid function

2. Ectopic thyroid tissue
   - may be found anywhere along the course of the thyroglossal duct
Pathology of thyroid

B. GOITER

A chronic enlargement of thyroid gland due to other than neoplasm

Synonym: STRUMA
B. GOITER

A. CAUSES

a. Physiologic enlargement
   - is not uncommon in puberty and pregnancy

b. Iodine deficiency
   - occurs in geographic areas where diet is deficient in iodine

c. Hashimoto thyroiditis

d. Goitrogens
   - foods or drugs that suppress synthesis of thyroid hormone

e. Dyshormogenesis
   - partial or complete failure of thyroid hormone synthesis; can be caused by various enzyme deficiencies
Pathology of thyroid

B. GOITER

B. TERMINOLOGY

a. Simple goiter (nontoxic goiter)
   - is goiter without thyroid hormone dysfunction

b. Toxic goiter
   - is goiter associated with hyperthyroidism

c. Endemic goiter
   - goiter occurring with high frequency in iodine-deficient geographic areas

d. Nodular goiter
   - irregular enlargement of the thyroid → nodule formation
   - nodular colloid goiter: late stage simple goiter, in which goiter is most often nodular (most nodules are hypoplastic and do not take up radioactive iodine → “cold” nodule)
Non-toxic goiter

Irregular nodules

Marked variation in the size of follicles
The gland is coarsely nodular and contains areas of fibrosis and cystic change.
C. HYPOTHYROIDISM

Diminished production of thyroid hormone, leading to clinical manifestation of thyroid insufficiency. It can be the consequences of three general processes:

- Defective synthesis of thyroid hormone, with compensatory goitrogenesis (goitrous hypothyroidism)
- Inadequate function of thyroid parenchyma (usually as a result of thyroiditis, surgical resection, or radioiodine therapy)
- Inadequate secretion of TSH by the pituitary or TRH by the hypothalamus
Pathology of thyroid

C. HYPOTHYROIDISM

Dominant clinical manifestation
Pathology of thyroid

C. HYPOTHYROIDISM

Laboratory abnormalities

1. Decrease serum free T4, increased serum TSH
2. Increase serum cholesterol
3. Classic thyroid test
   - T3 resin uptake → decreased
   - Total T4 → decreased
Pathology of thyroid

C. HYPOTHYROIDISM

Clinical syndromes

Hypothyroidism is manifest as Myxedema in adults or as Cretinism in children
Pathology of thyroid: **C. HYPOTHYROIDISM:**

**Myxedema**

A. More common in women

B. Etiology:

1. Therapy for hyperthyroidism with surgery, irradiation, or drugs
2. Hashimoto thyroiditis
3. Unknown – primary idiopathic myxedema – is a poorly defined form of myxedema: TSH receptor blocking antibodies have been identified.
4. Iodine deficiency is the most important cause in non-iodine deficient geographic regions
Pathology of thyroid: **C. HYPOTHYROIDISM:**

**Myxedema**

**C. Clinical characteristics**

1. Incidious onset
2. Cold intolerance
3. Tendency to gain weight because of a low metabolic rate
4. Lowered pitch of voice
5. Mental and physical slowness
6. Menorrhagia
7. Constipation
8. Abnormal physical findings:
   - puffiness of face, eyelids, and hands
   - dry skin
   - hair loss; coarse and brittle hair; scant axillary and pubic hair; thinning of the lateral aspect of the eyebrows
   - increase in relaxation phase of deep tendon reflexes.
Pathology of thyroid: **C. HYPOTHYROIDISM:**

**CRETINISM**

**A. Etiology:**
1. Iodine deficiency
2. Deficiency of enzymes necessary for the synthesis of thyroid hormones
3. Maldevelopment of the thyroid gland
4. Failure of the fetal thyroid to descend from its origin at the base of the tongue
5. Trans placental transfer of antithyroid antibodies from a mother with autoimmune thyroid disease

**B. Characteristics:**
1. Severe mental retardation
2. Impairment of physical growth with retarded bone development and dwarfism
3. Large tongue
4. Protuberant abdomen
A. Clinical Features

1. Restlessness, irritability, fatigability
2. Tremor
3. Heat intolerance; sweating; warm, moist skin (especially palms)
4. Tachycardia, often with arrythmia and palpitation, sometimes with high-output cardiac failure
5. Muscle wasting and weight loss despite increase appetite
6. Fine hair
7. Diarrhea
8. Menstrual abnormalities, commonly amenorrhoea or oligomen.
9. Greatly increased free T4 and reduced TSH and less commonly employed are increased total T4&T3, and resin uptake
Graves disease, hyperthyroidism

Exophthalmos

Thyroid mass
Major clinical manifestations of Graves disease
HYPERTHYROIDISM (THYROTOXICOSIS)

B. Graves Disease

General Characteristics
1. Hyperthyroidism caused by diffuse toxic goiter
2. Associated with striking exophthalmos → autoimmune?
3. More in women
4. Incidence increased in HLA-DR3 and HLA-B8 positive individual

Mechanism
1. Thyroid-stimulating-immunoglobulin (TSI) → reacts with TSH receptors → stimulates thyroid hormone production
2. Thyroid-growth-immunoglobulin (TGI) → stimulates glandular hyperplasia and enlargement
3. Antimicrosomal and other autoantibodies are characteristic
Pathology of thyroid

HYPERTHYROIDISM (THYROTOXICOSIS)

B. Other causes of hyperthyroidism

1. Plummer Disease
   - the combination of hyperthyroidism, nodular goiter, and absence of exophthalmos
   - the “hot” nodules can be adenomas or non-neoplastic areas of nodular hyperplasia

2. Pituitary hyperfunction
   - can cause excess production of TSH and secondary hyperthyroidism

3. Struma ovarii
   - ovarian teratoma made up of thyroid tissue, can be hyperfunctional

4. Exogenous administration of thyroid hormone
Graves Disease

Diffusely hyperplastic thyroid with follicle are lined by tall, columnar epithelium, and scalloped (“moth eaten”) appearance of the edge of the colloid.
Graves disease, hyperthyroidism

The follicles are lined by hyperplastic, tall columnar cells
Immune mechanism of Graves Disease and Hashimoto Thyroiditis
E. THYROIDITIS

Inflammation of the thyroid gland
(encompasses a heterogenous group of inflammatory disorders of the thyroid gland, including those that are caused by autoimmune mechanisms and infectious agents)

A. Acute suppurative thyroiditis: a bacterial infection, usually occurs in young children or debilitated patients. It is rare
B. Subacute granulomatous thyroiditis (De Quervain thyroiditis)
C. Chronic thyroiditis (Hashimoto thyroiditis, Struma lymphomatosas, autoimmune thyroiditis)
D. Riedel’s struma (Riedel’s disease)
Subacute/De Quervain/Granulomatous Thyroiditis

- Is characterized by focal destruction of thyroid tissue and granulomatous inflammation
- Etiology: variety of viral infections such as mumps or coxsackie virus
- Follows a limited course several weeks of duration consisting of flu-like illness along with pain and tenderness of the thyroid, sometimes with transient hyperthyroidism
- More common in women
The release of colloid into the interstitial tissue has elicited a prominent granulomatous reaction, with numerous foreign body giant cells
Subacute/De Quervain/Granulomatous Thyroiditis

The parenchyma contains chronic inflammatory infiltrate with a multinucleate giant cells and colloid follicles
Chronic autoimmune (Hashimoto) thyroiditis

- Autoimmune disorder that occur more often in women
- Common cause of hypothyroidism, may occasionally have an early transient hyperthyroid phase
- Characterized histologically by massive infiltrates of lymphocytes with germinal center formation, thyroid follicles are atrophic, and Hurthle cells are prominent
- Associated with various antibodies (antithyroglobulin, antithyroid peroxidase, anti TSH-receptor, anti-iodine receptor antibodies)
- May be associated with other autoimmune disorders: pernicious anemia, DM, Sjogren syndrome → the incidence is increased in HLA-DR5 and HLA-B5 positive
Chronic autoimmune (Hashimoto) thyroiditis

The thyroid gland is symmetrically enlarged and coarsely nodular. Coronal section → irregular nodules and an intact capsule.
Chronic autoimmune (Hashimoto) thyroiditis

Atrophic thyroid follicles with conspicuous chronic inflammatory infiltrate (the inflammatory cells form prominent lymphoid follicles with germinal centers)
Hashimoto Thyroiditis

Dense lymphocytic infiltrates with germinal centers
Residual thyroid follicle lined by Hurthle cells are also seen
Riedel thyroiditis

- Characterized by thyroid replacement of fibrous tissue
- Etiology is unknown, does not appear to be related to other thyroiditis
- Also involves extra thyroidal soft tissue of the neck, often associated with fibrosis in other location (retroperitoneum, mediastinum, orbit)
- May clinically mimic carcinoma
Riedel thyroiditis

The thyroid parenchyma is largely replaced by dense, hyalinized fibrous tissue and a chronic inflammatory infiltrate
F. BENIGN TUMORS (ADENOMAS)

- Are most often solitary
- Present clinically as nodules
- Can occur in a variety of histologic pattern (follicular, Hurthle cell)
- Are most often nonfunctional but can occasionally cause hyperthyroidism
- Female:male is 7:1
FOLLICULAR ADENOMA

- Embryonal adenoma
- Fetal adenoma
- Simple adenoma
- Colloid adenoma
- Hurthel cell adenoma
- Atypical adenoma
Follicular adenoma

Embryonal adenoma

The tumor features a trabecular pattern with poorly formed follicles that contain little if any colloid.
The cut surface of an encapsulated mass reveals:

- Hemorrhage
- Fibrosis
- Cystic change
A solitary, well-circumscribed nodule is seen.
Follicular Adenoma

Well-differentiated follicles resembling normal thyroid parenchyma.
Follicular adenoma

FETAL ADENOMA

Regular pattern of small follicles
Follicular adenoma

Hurthle cell Adenoma

Cells with abundant eosinophilic cytoplasm and small regular nuclei.
Pathology of thyroid

G. MALIGNANT TUMORS

- Papillary Carcinoma
- Follicular Carcinoma
- Medullary Carcinoma
- Anaplastic Carcinoma
Papillary Thyroid Carcinoma (PTC)

- Is the most common thyroid cancer (90%)
- Most frequent between ages 20 – 50 years
- Female:male is 3:1
- Papillary growth pattern with ground glass nuclei
- Better prognosis than other forms of thyroid cancer, even when adjacent lymph nodes is involved
- Can be long-term consequence of prior radiotherapy to the neck
- Typically invades lymphatics and spreads to regional lymph nodes
G. MALIGNANT TUMORS

Papillary Thyroid Carcinoma (PTC)

Pathogenesis:

• Iodine excess
  Animal exp., in endemic goiter region addition of iodine → increase incidence

• Radiation
  Radiation therapy, and radioactive ray

• Genetic factors
  First degree relatives of persons with tumor: 4-10 fold higher risk

• Somatic mutation
  Somatic rearrangement of RET protooncogene in chromosome 10 (10q11.2)
Papillary Thyroid Carcinoma (PTC)

Macroscopic appearance with grossly discernible papillary structure

FNAB - BAJAH
G. MALIGNANT TUMORS

Papillary Thyroid Carcinoma (PTC)

Cut surface displays a circumscribed pale tan mass with foci of cystic change
Well-formed papillae

“Orphan Annie eye”, or ground-glass nuclei, or empty appearing nuclei
G. MALIGNANT TUMORS

Papillary Thyroid Carcinoma (PTC)
the most common thyroid cancer

Branching papillae are lined by neoplastic columnar epithelium with clear nuclei. A calciospherite (psammoma body) is evident.
Follicular Thyroid Carcinoma (FTC)

- FTC is defined as a malignant neoplasm that is purely follicular and does not contain papillary or any other elements.
- Mostly are detected as a palpable nodule or enlarged thyroid, or as advanced form as bone (pathological fracture), or lung metastasis.
- Poorer prognosis than PTC.
- Differs from PTC in that metastases are blood borne rather than lymphatic, directed principally to the bones of shoulder and pelvic girdles, sternum, and skull.
G. MALIGNANT TUMORS

Follicular Thyroid Carcinoma FTC)

Cut surface of follicular carcinoma with the substantial replacement of the lobe of the thyroid.

The tumor has a light-tan appearance and contains small foci of hemorrhage.
G. MALIGNANT TUMORS

Follicular Thyroid Carcinoma (FTC)

Glandular lumen contains recognizable colloid
Capsular integrity in follicular neoplasm is critical in distinguishing follicular adenoma from carcinoma.

**Follicular adenoma:** capsule is usually thin, occasionally more prominent; no capsular invasion is seen (arrows).

**Follicular carcinoma:** capsular invasion (arrows)
A microfollicular tumor has invaded veins in the thyroid parenchyma.
G. MALIGNANT TUMORS

Medullary Thyroid Carcinoma (MTC)

- MTC is distinguished by its secretion of the calcium-lowering hormone (calcitonin)
- Represents no more than 5% of all thyroid cancers
- 80% are sporadic form: RET protooncogene mutation are detected in 25-70% of cases
- 20% are familial form: afflicted by MEN type 2 → includes phaeochromocytoma and parathyroid hypoplasia, adenoma
- The mean age: 50 years (familial case 20 years)
G. MALIGNANT TUMORS

Medullary Thyroid Carcinoma (MTC)

- Tends to arise in superior portion (the region that are richest in C cells--parafollicular)
- Often multicentric and bilateral (MEN setting)
- Conspicuous feature: the presence of stromal amyloid, representing the disposition of calcitonin
- The preccursor of the familial form MTC is C cell hyperplasia
- Tumor markers: Calcitonin, CEA, Chromogranin
G. MALIGNANT TUMORS: Medullary Thyroid Carcinoma (MTC)

Clinical Features

- Symptoms related to endocrine secretion: carcinoid syndrome (calcitonin), Cushing syndrome (ACTH)
- Watery diarrhea in 1/3 cases, caused by secretion of vasoactive intestinal peptide, pros-taglandin, and several kinins
- Familial MTC: hypertension, episodic hypertension, symptoms attributable to the secretion of catecholamines and phaeochromocytoma
- Therapy: thyroidectomy → local recurrences 1/3
- 5-year survival rate is 75%
G. MALIGNANT TUMORS:

Medullary Carcinoma

Solid pattern of growth and do not have connective tissue capsule.

Coronal section → total (bilateral) involvement by a firm, pale tumor.
G. MALIGNANT TUMORS:

Medullary Thyroid Carcinoma

Nest of polygonal cells embedded in a collagenous framework.
G. MALIGNANT TUMORS:

Medullary Thyroid Carcinoma

Amyloid: Congo red staining → polarized light microscope  
→ pale green birefringent
G. MALIGNANT TUMORS:

Medullary Carcinoma

Typically contain amyloid, visible here as homogenous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells.
G. MALIGNANT TUMORS:

Anaplastic (Undifferentiated) Carcinoma of the Thyroid

• Usually fatal, principally afflict women (4:1) over the age of 60 years
• Constitutes 10% of thyroid cancers
• It seems likely that the anaplastic carcinoma represent the transformation of a benign or lower grade thyroid neoplasm into poorly differentiated and highly aggressive cancer
• Mutation of p53 is common
• 5-year survival rate less than 10%
The tumor in traverse section partially surround the trachea and extend into the adjacent soft tissue.
G. MALIGNANT TUMORS:

Anaplastic Carcinoma

The tumor is composed of bizarre spindle and giant cells with numerous mitoses
G. MALIGNANT TUMORS:

Lymphoma of the thyroid

- Are largely B-cell tumors
- Accounts for 2% of all thyroid cancers
- Most if not all cases arise in the setting of chronic thyroiditis
- More in women (4:1), the mean age is older than men
- Macros: large, soft, tannish masses of thyroid, usually extending beyond the confines of gland
- Micros: same spectrum as other sites, mostly diffuse large cell pattern