Pathology of endocrine

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DISEASES OF THE ENDOCRINE GLANDS

THYROID GLAND

Diseases of the thyroid gland are generally more common in females.

HYPERTHYROIDISM

Thyrotoxicosis is a hypermetabolic state caused by elevated circulating levels of free T3 and T4. Because it is caused most commonly by hyperfunction of the thyroid gland, it is often referred to as hyperthyroidism. However, in certain conditions the oversupply is related to either excessive release of preformed thyroid hormone (e.g., in thyroiditis) or to an extrathyroidal source, rather than hyperfunction of the gland

Table 24.3 Disorders Associated With Thyrotoxicosis

Associated With Hyperthyroidism
Primary
Diffuse hyperplasia (Graves disease)
Hyperfunctioning ("toxic") multinodular goiter
Hyperfunctioning ("toxic") adenoma
Iodine-induced hyperthyroidism
Neonatal thyrotoxicosis associated with maternal Graves disease
Secondary
TSH-secreting pituitary adenoma (rare)[a]
Not Associated With Hyperthyroidism
Granulomatous (de Quervain) thyroiditis (painful)
Subacute lymphocytic thyroiditis (painless)
Struma ovarii (ovarian teratoma with ectopic thyroid)
Factitious thyrotoxicosis (exogenous thyroxine intake)

Clinical pictures:

wide variety of signs and symptoms, including:

- *Unintentional weight loss, even when your appetite and food intake stay the same or increase.*
- *Rapid heartbeat (tachycardia) — commonly more than 100 beats a minute.*
- *Irregular heartbeat (arrhythmia).*
- *Pounding of your heart (palpitations).*
- *Increased appetite.*
- *Nervousness, anxiety and irritability.*
- *Tremor — usually a fine trembling in your hands and fingers.*
- *Sweating.*

- *Changes in menstrual patterns.*
- *Increased sensitivity to heat.*
- *Changes in bowel patterns, especially more frequent bowel movements.*
- *An enlarged thyroid gland (goiter), which may appear as a swelling at the base of your neck.*
- *Fatigue, muscle weakness.*
- *Difficulty sleeping.*
- *Skin thinning.*

HYPOTHYROIDISM

Hypothyroidism is a condition caused by a structural or functional derangement that interferes with the production of thyroid hormone.
Hypothyroidism is a common disorder.
By some estimates, the prevalence of overt hypothyroidism is 0.3%, while that of subclinical hypothyroidism is greater than 4%. The prevalence increases with age, and it is nearly 10-fold more common in women than in men.
Hypothyroidism can result from a defect anywhere in the hypothalamic-pituitary-thyroid axis. Like hyperthyroidism, it can be divided into primary and secondary forms,

Table 24.4 Causes of Hypothyroidism

Primary
Genetic defects in thyroid development (*PAX8*, *FOXE1*, TSH receptor mutations; rare)
Thyroid hormone resistance syndrome (*THRB* mutations; rare)
Postablative
Surgery, radioiodine therapy, or external irradiation
Autoimmune hypothyroidism
Hashimoto thyroiditis[a]
Iodine deficiency[a]
Drugs (lithium, iodides, p-aminosalicylic acid)[a]
Congenital biosynthetic defect (dyshormonogenetic goiter; rare)[a]
Secondary ("Central Hypothyroidism")
Pituitary failure (rare)
Hypothalamic failure (rare)

Clinical features

The signs and symptoms of hypothyroidism vary, depending on the severity of the hormone deficiency. Problems tend to develop slowly, often over a number of years. signs and symptoms may include:

- *Fatigue.*
- *Increased sensitivity to cold.*
- *Constipation.*
- *Dry skin.*
- *Weight gain.*
- *Puffy face.*
- *Hoarseness.*
- *Muscle weakness.*
- *Elevated blood cholesterol level.*

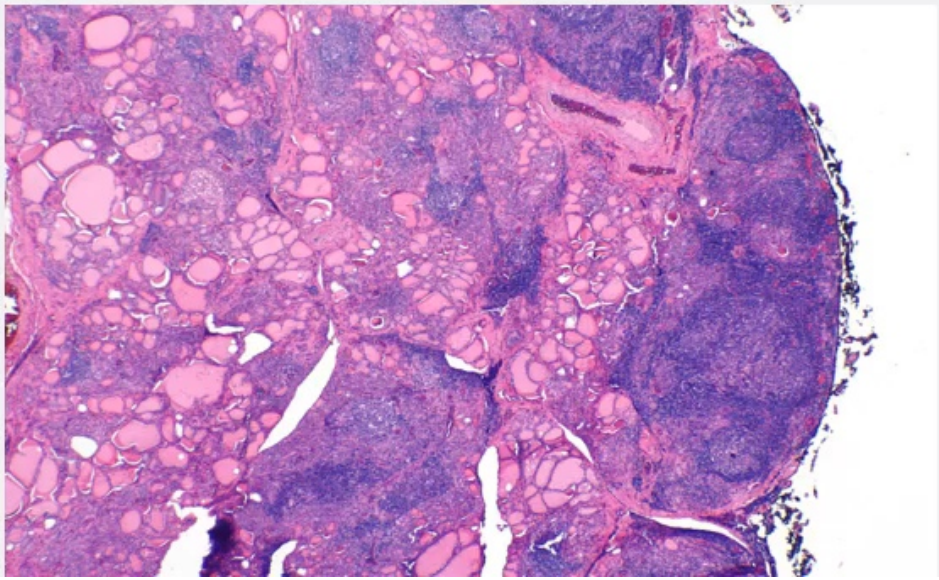
- *Muscle aches, tenderness and stiffness.*
- *Pain, stiffness or swelling in your joints.*
- *Heavier than normal or irregular menstrual periods.*
- *Thinning hair.*
- *Slowed heart rate.*
- *Depression.*
- *Impaired memory.*
- *Enlarged thyroid gland (goiter).*

THYROIDITIS

1-Hashimoto's Thyroiditis:

Aetiology: Autoimmune. The most likely mechanism of thyroid cell destruction is by cytotoxic T cell-mediated hypersensitivity reaction.

Gross: Symmetrically enlarged, firm rubbery gland. The normal red brown color of the gland is replaced by pale greyish white appearance.



Microscopy:

1-Extensive replacement of the thyroid by lymphocytes, which may sometimes form follicles.

2-Marked atrophy of the follicular epithelium. The residual follicular cells are commonly transformed into large pink cells (Askanazy or Hurthle cells).

Complications:

1-Myxoedema.

2- primary thyroid Lymphoma .

2-Riedel's Thyroiditis:

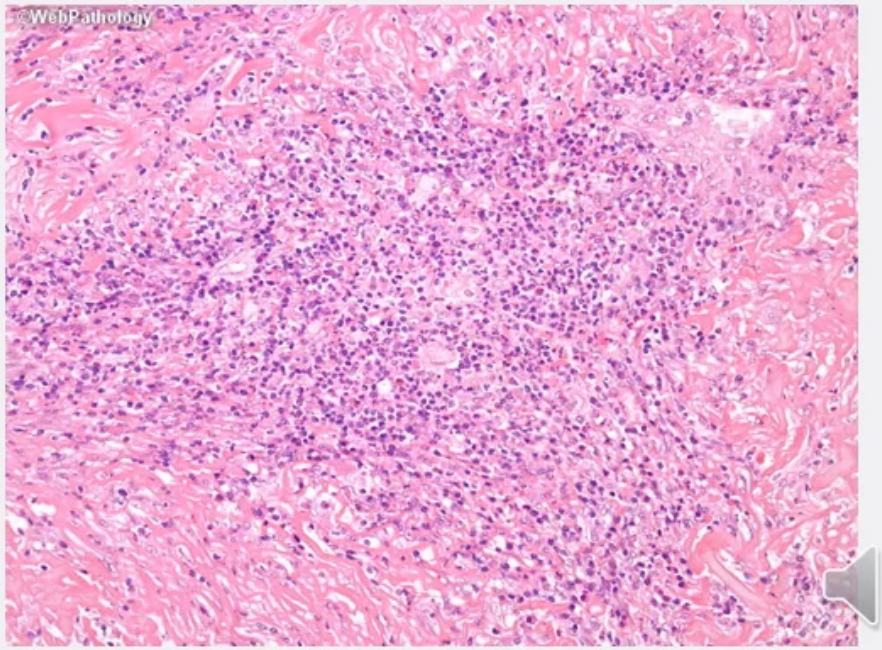
Aetiology: Idiopathic.

Gross: Enlarged, adherent, stony hard, greyish thyroid.

Microscopy: Inflammatory fibrosclerosis:

1-Patchy chronic inflammatory cell infiltrates associated with:

2-Patchy dense fibrosis and hyalinosis.



Complications:

1-Myxoedema.

2-Severe pressure symptoms.

3-Granulomatous (Subacute or de Quervain's Thyroiditis:

Aetiology: Unknown, but a viral aetiology is considered most likely.

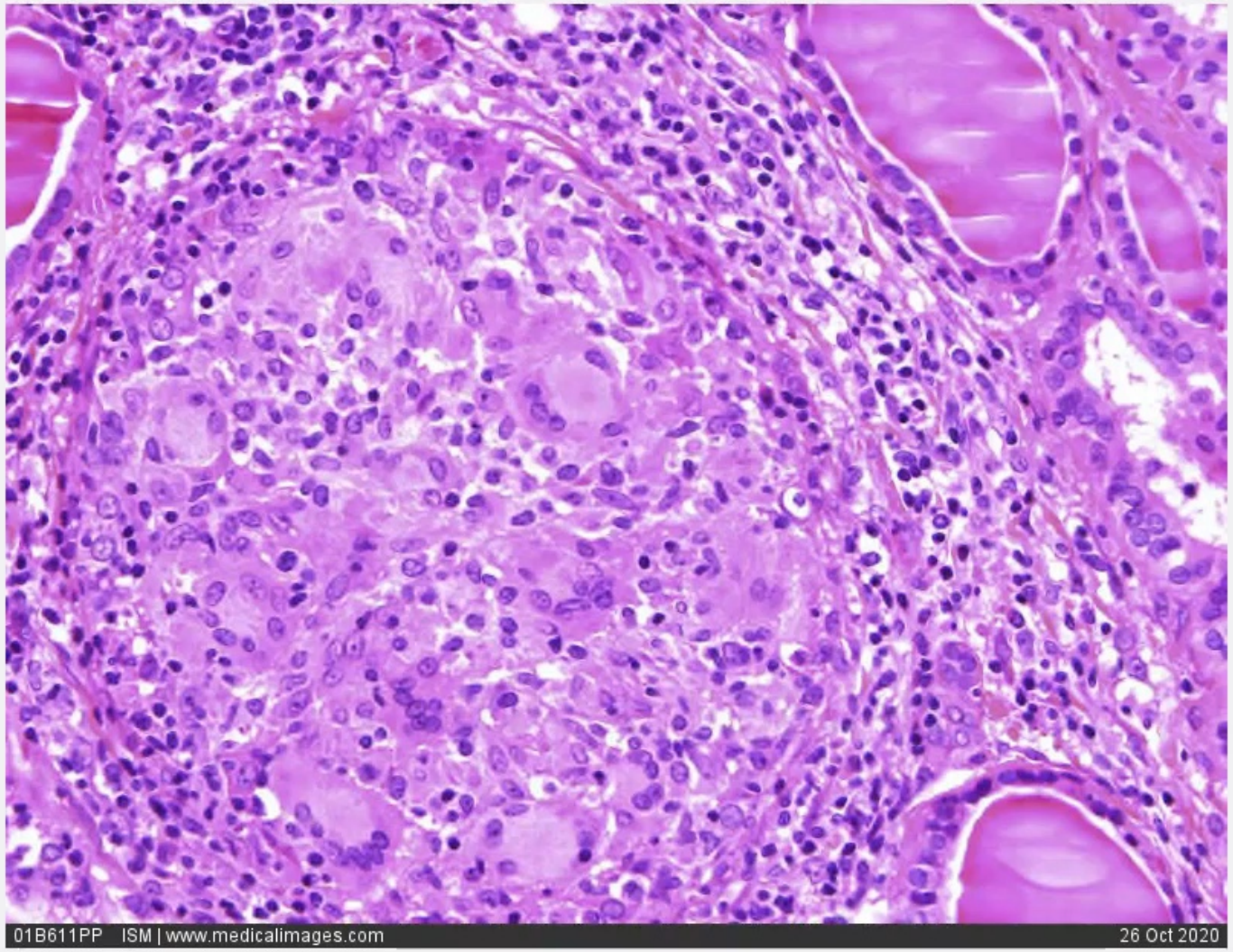
Gross: Enlarged non-adherent firm greyish thyroid.

Microscopy: Numerous granulomas rich in foreign body giant cells with extensive destruction and fibrosis of thyroid follicles.

Effects: Mild myxoedema.

4-Acute thyroiditis This is suppurative inflammation (abscess) *caused by pyogenic bacteria*

5-Other Types : *Tuberculous, syphilitic & fungal thyroiditis.*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GOITER

DEFINITION: Enlargement of thyroid gland not due to inflammation or tumors.

TYPES:

1-Simple goiter (non-toxic goiter): *a)Diffuse b) Nodular*

2-Toxic goiter: *a) Primary type (Grave's disease, exophthalmic goiter). b)Secondary type*

1-SIMPLE GOITER

Definition: This is goiter ,unaccompanied by thyroid hyperfunction (non toxic goiter)

Aetiology: Iodine deficiency which may be :

1-Absolute deficiency (Endemic type):

Occurs in parts of the world deficient in iodine .The use of iodinated salt in these areas has markedly reduced the incidence of goiter.

Regular consumption of goitrogenic substances is another possible factor. Examples of goitrogenes include calcium and fluorides in the water supply and thiocyanates in food (Cabbage, cauliflower...).

2-Relative deficiency (Sporadic type): *affecting females because of their high iodine demand (due to iodine loss in menses and during pregnancy and lactation).*

Pathology:

1-Diffuse Goiter: (Parenchymatous Goiter ,Colloid Goiter):

Aetiology and pathogenesis:

lodine deficiency → decrease in the output of thyroid hormones – rise of TSH → diffuse thyroid hyperplasia → thyroid enlargement (and rise of hormone output).

Early enlargement may be called parenchymatous goiter, but with persistent iodine deficiency, thyroid is considerably enlarged due to colloid distention of thyroid follicles and this is called colloid goiter.

Gross: There is diffuse symmetrical thyroid enlargement.Cut section shows:

In parenchymatous goiter: Fleshy grayish pink appearance.

In colloid goiter: Microcystic spaces filled with brownish gelatinous colloid.

Microscopy:

In parenchymatous goiter: Mildly enlarged thyroid follicles, filled with little colloid & lined by hyperplastic cuboidal epithelium.

In colloid goiter: Markedly enlarged follicles , distended with abundant colloid & lined by flattened epithelium.

2-Nodular Goiter:

Aetiology and pathogenesis:

Nodular goiter may develop on top of diffuse goiter, but the exact pathogenesis is unclear. It is believed that nodular goiter is due to repeated cycles of iodine deficiency (thyroid hyperplasia) and iodine correction (thyroid involution) which create an abnormal gland rhythm accompanied by irregular vascularity, irregular hyperplasia and irregular fibrosis leading to formation of one or commonly multiple nodules (multinodular goiter).

Gross:

Asymmetrically enlarged thyroid.

The outer surface and cut section are multinodular. The nodules are variable-sized and separated by fibrous tissue. Some nodules are firm , others show a gelatinous colloid pattern. Secondary changes are common including cystic changes, hemorrhage and dystrophic calcification.

Microscopy: *The thyroid follicles within the nodules are very variable reflecting the abnormal gland rhythm; some follicles appear normal, others are hyperplastic or colloid- distended. Cystic follicles are common and may show hyperplastic papillary epithelial projections. Hemorrhage and calcification are common. The nodules are separated by fibrous tissue infiltrated by lymphocytes.*

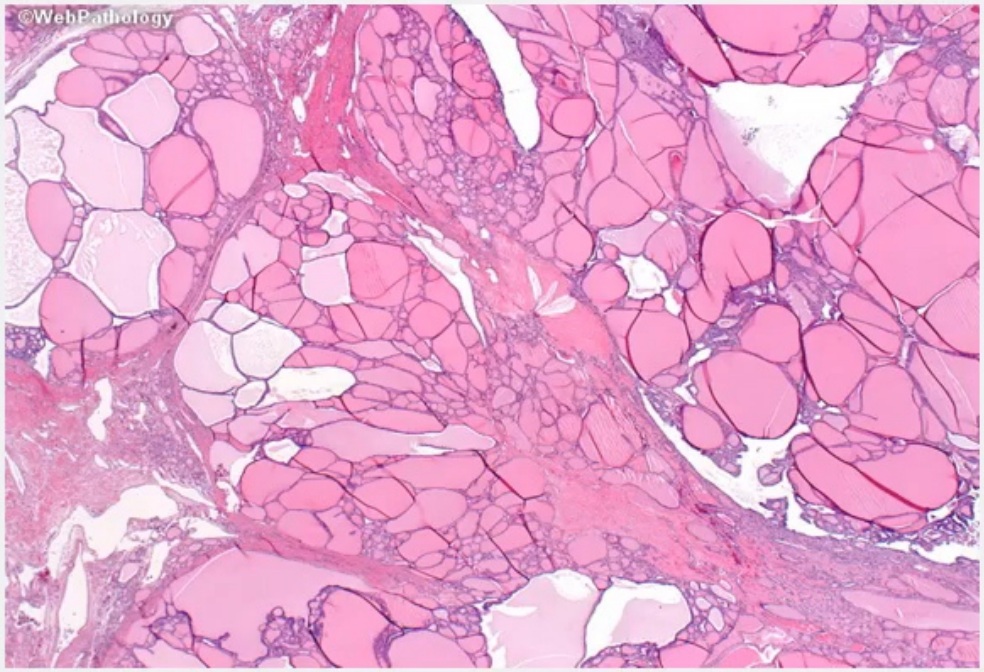
Complications:

a)Pressure effects.

b)Retrosternal extension.

c)Toxic transformation (secondary or toxic nodular goiter).

d) Malignant change is questionable.



2-GRAVE'S DISEASE
(Diffuse toxic goiter or Exophthalmic goiter)

Pathogenesis:

Grave's disease is an autoimmune disease characterized by hyperthyroidism associated with exophthalmos. It was formerly believed to be due to the presence of an autoantibody termed LATS (long acting thyroid stimulator). Nowadays it is believed to be caused by a complex group of autoantibodies, the most important of which are:

1-Thyroid stimulating immunoglobulins (TSI): They act on TSH receptors mimicking the action of TSH.

2-Thyroid growth stimulating immunoglobulins (TGI): These initiate the growth of thyrocytes.

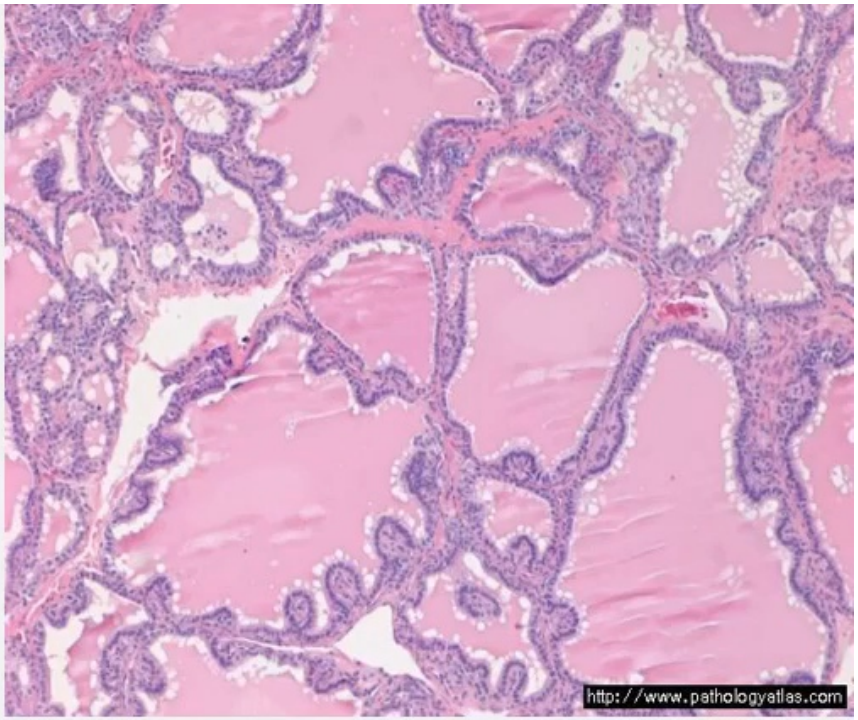
The mechanism of exophthalmos is obscure. However it was found that TSI has a fibroblast stimulating action and it is thought that it stimulates the fibroblastic proliferation of the retro-orbital tissues leading to exophthalmos.

Pathological features:

A-Pathology of the thyroid gland

Gross: Moderate diffuse symmetrical thyroid enlargement

The cut section is pink due to high vascularity.



Microscopy:

1-Thyroid Follicles:

a)The follicles are hyperplastic, their lining is tall columnar with frequent papillary formation.

b) They contain small amount of colloid which is peripherally scalloped (vacuolated).

This is due to rapid absorption of thyroid hormones.

2-Thyroid Stroma shows:
a)Excess vascularity.
b)Lymphocytic infiltrates.

B-Other pathological features

1-Exophthalmos: protrusion of eyeballs with risk of ocular infection and blindness.
2-Loss of weight
3-Tremors
4-Left ventricular hypertrophy, tachycardia.
5-Pretibial myxoedema occur in 5% of patients due to localized accumulation of mucopolysaccharides forming circumscribed patches in the pretibial skin.

6-Diffuse lymphoid hyperplasia of lymphoid organs as thymus and spleen.

7-Blood: relative lymphocytosis and may be neutropenia.

Remark: Causes Of Thyrotoxicosis (Hyperthyroidism):

1-Grave's disease.

2-Toxic nodular goiter.

3-Toxic adenoma

4-Hashitoxicosis (a combination of Grave's disease and Hashimoto's disease)

BENIGN TUMORS (ADENOMA)

GROSS: *A solitary round encapsulated nodule up to 5 cm. in diameter. Cut section is fleshy grayish pink. Secondary changes including hemorrhage, fibrosis, calcification and cystic changes are common.*

MICROSCOPY:

1-Follicular Adenoma:

Many histological types :

a)Normofollicular adenoma: composed of normal-sized follicles.

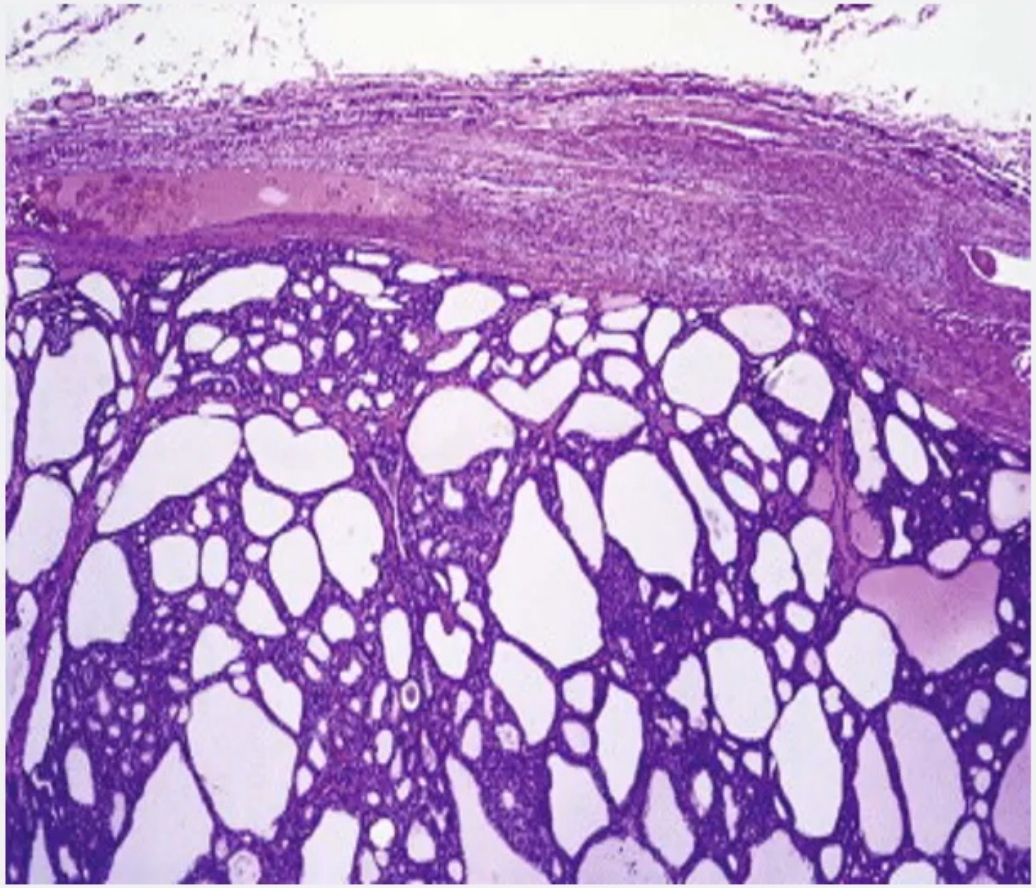
b)Macrofollicular adenoma (colloid adenoma): composed of large-sized follicles distended with colloid.

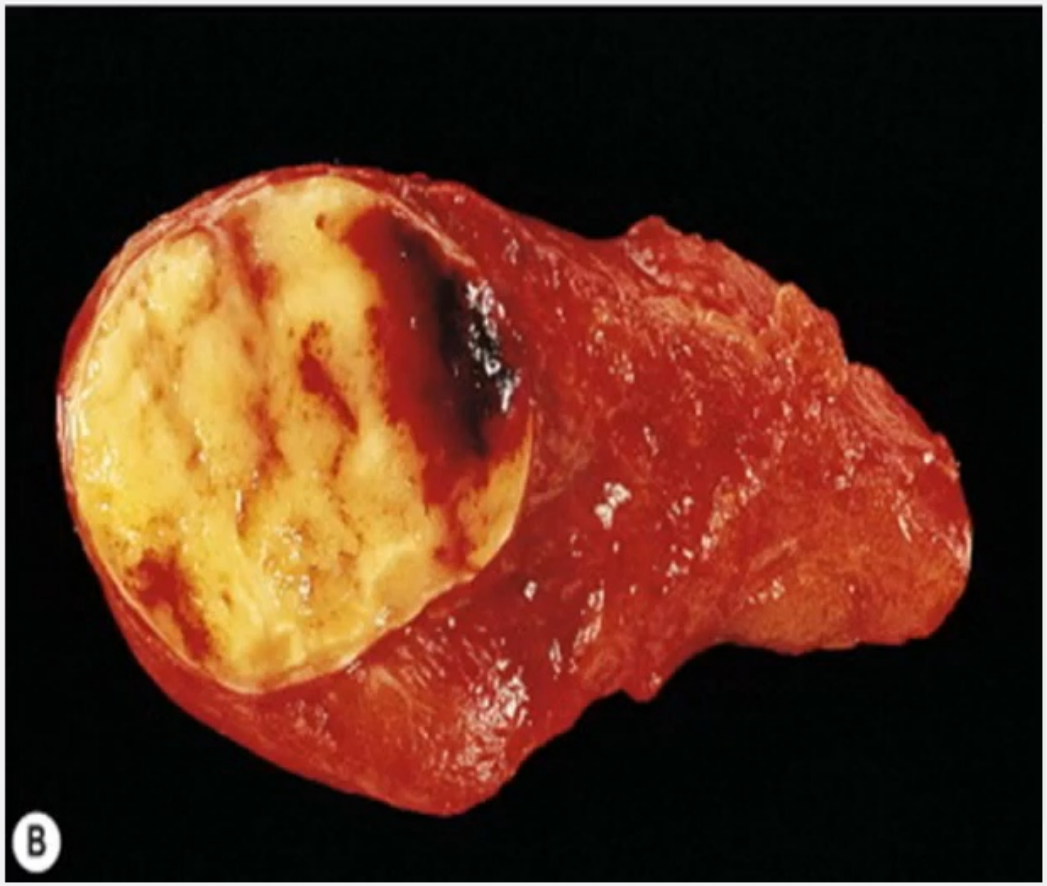
c)Microfollicular adenoma (fetal or embryonal adenoma)composed of very small follicles

d) Hurthle cell adenoma :composed of follicles lined by large polyhedral eosinophilic cells having abundant pink granular cytoplasm (Hurthle cells).

All follicular adenomas are surrounded by a complete fibrous capsule of varying thickness and the normal thyroid parenchyma around the adenoma is compressed. The capsule is intact and there is no vascular invasion. Absence of capsular and vascular invasions is the criterion used to differentiate follicular adenoma from well differentiated follicular carcinoma.

2-Atypical adenoma: *Shows cellular pleomorphim and atypia (but with no vascular invasion)*

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THYROID CARCINOMA

SEX & AGE: *More common in females. Most tumors arise in elderly (above the age of 50 years), but papillary carcinoma may also arise in children & young adults before the age of 20 years*

PREDISPOSING FACTORS:

1-lonizing radiation

2-Thyroid adenoma

GROSS:

A greyish irregular firm infiltrating growth which may exceed 10 cm in diameter

May also occur in the form of a small or large circumscribed nodule or multicentric nodules. Although malignant, some tumors are encapsulated. Areas of hemorrhage, necrosis, cystic changes and calcifications may occur.

PATHOLOGICAL TYPES:

1-Papillary carcinoma (best prognosis):

The most common type of thyroid carcinoma about 80%

May arise at any age including children and young adults.

The malignant cells form cystic spaces showing papillary projections, lined by malignant cells that characteristically show optically clear nuclei with prominent nuclear grooves

The tumor is frequently associated with calcified bodies (psammoma bodies).

Distant spread is mainly by lymphatics, Blood spread is very rare & late. The tumor has the best prognosis among all types of thyroid carcinoma.

ONCOGENE ALTERNATION:

- *Point mutation BRAF, exon 15 (up to 60%).*
- *Translocations of RET proto-oncogene with multiple different genes (RET/PTC gene rearrangements, 30%, although higher percentage in children).*
- *N-ras mutations particularly follicular variant (10%).*
- *TRK gene rearrangements with multiple genes (10%).*

● *New tyrosine kinase inhibitors affect the BRAF and RET pathways and may provide targeted therapy for patients with aggressive disease or distant metastases.*

2-Follicular carcinoma:

Usually arises in elderly individuals.

It is characterized microscopically by follicles (acini) lined by malignant cells, showing dark nuclei. Mitoses are mainly detected in less differentiated forms. Well differentiated follicular carcinoma may grossly and microscopically resemble follicular adenoma.

Diagnosis of malignancy in these cases is made when there is capsular and/ or vascular invasion

Distant spread is mainly by blood & metastases are common in lungs and bone.

Usually poor prognosis.

3-Hurthle cell carcinoma: *Characterized by malignant eosinophilic cells.*

4-Anaplastic carcinoma: *Composed of highly malignant spindle or giant cells.*

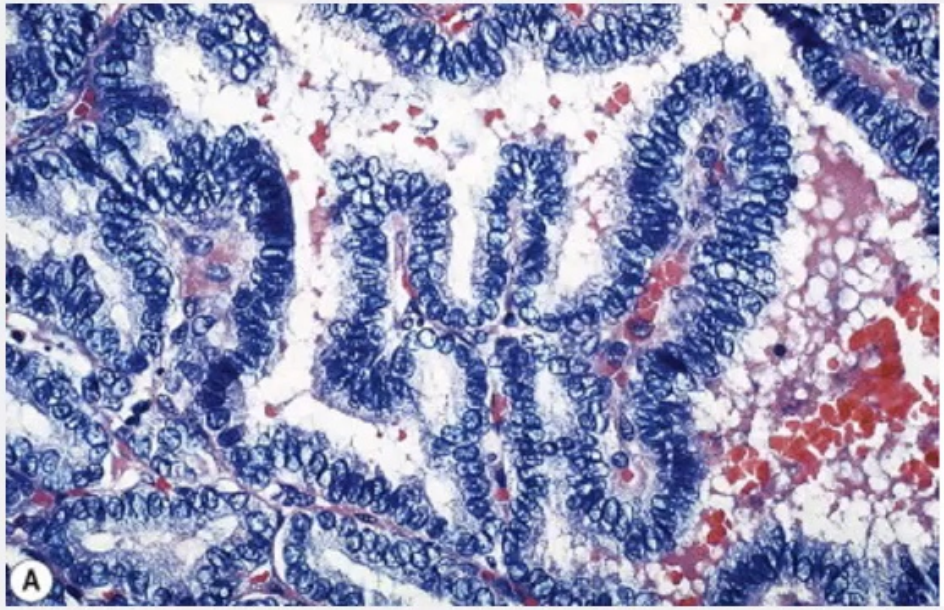
5-Medullary carcinoma:

Arises from parafollicular cells (C cells).

Consists of malignant polyhedral cells separated by stroma containing amyloid.

May be associated with paraneoplastic syndromes (carcinoid or Cushing syndrome)

Prognosis is better than follicular carcinoma.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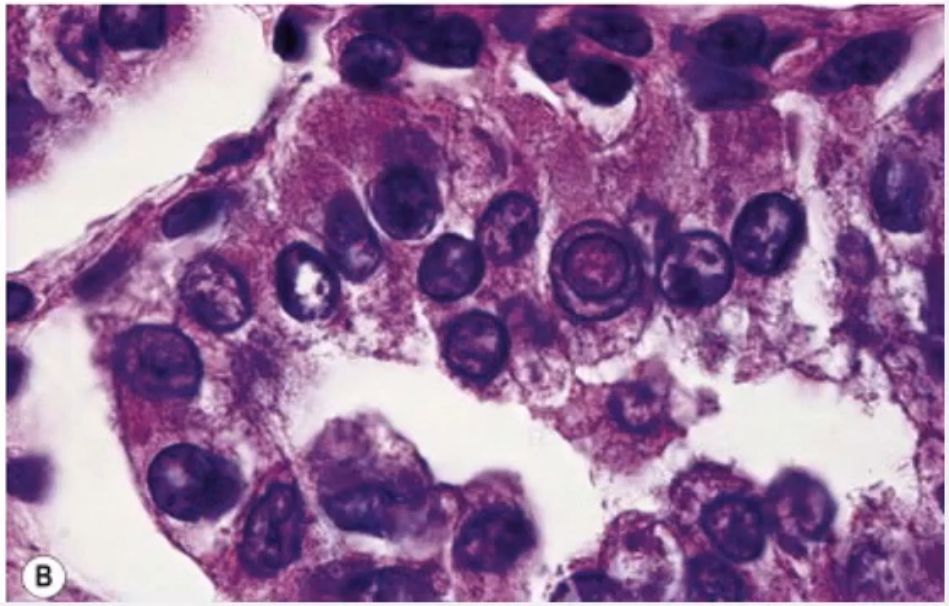
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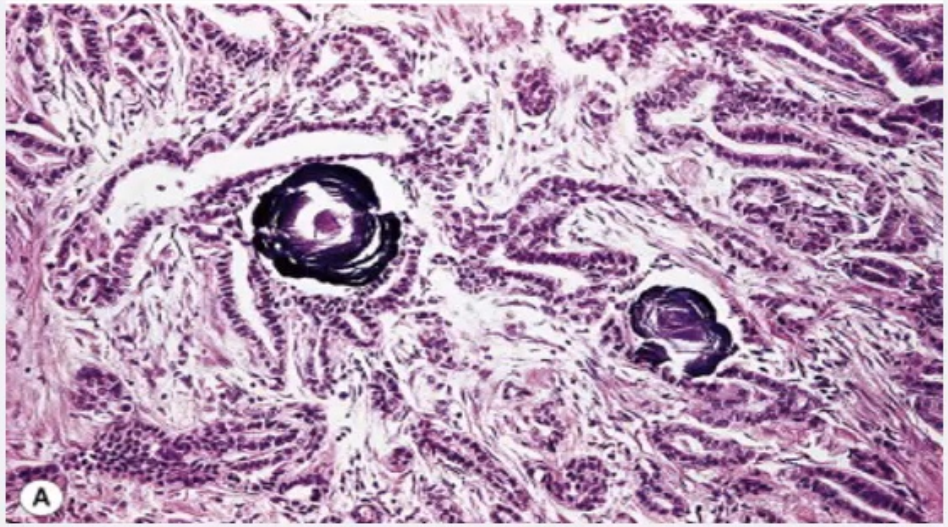
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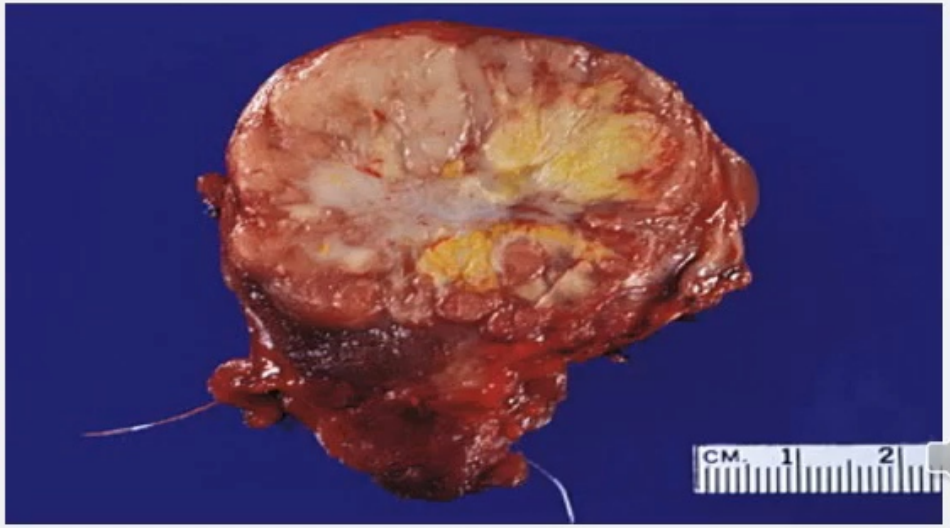
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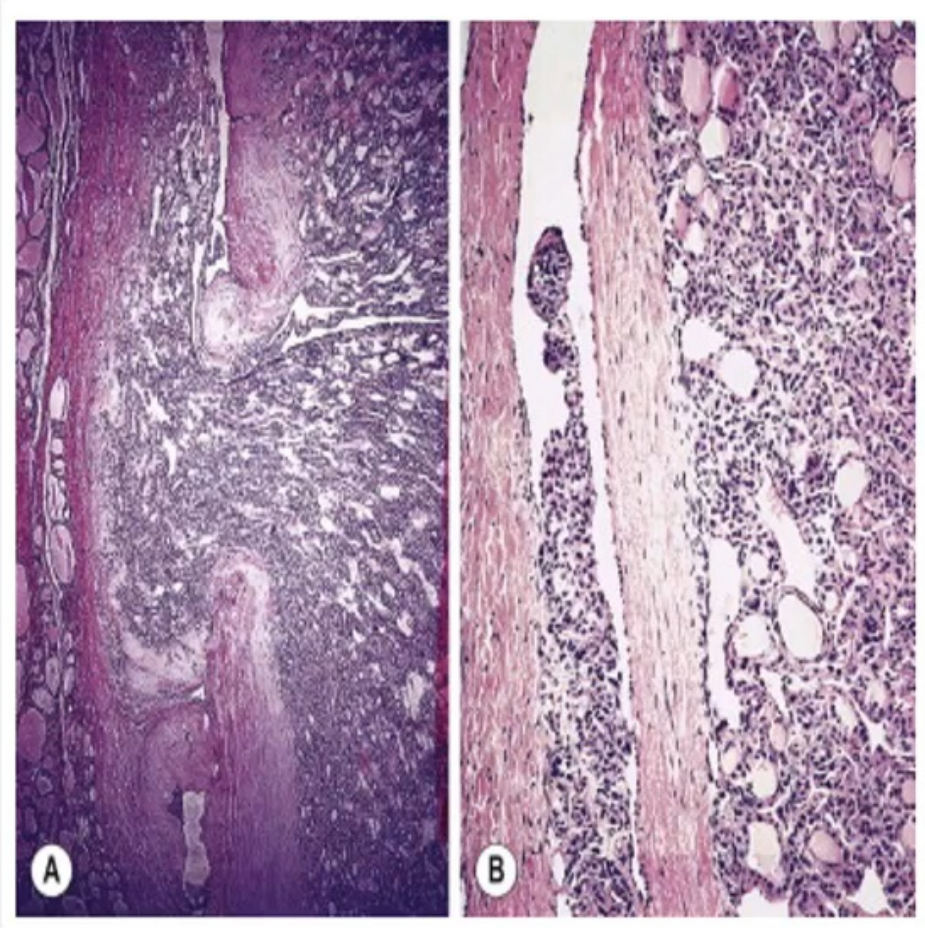
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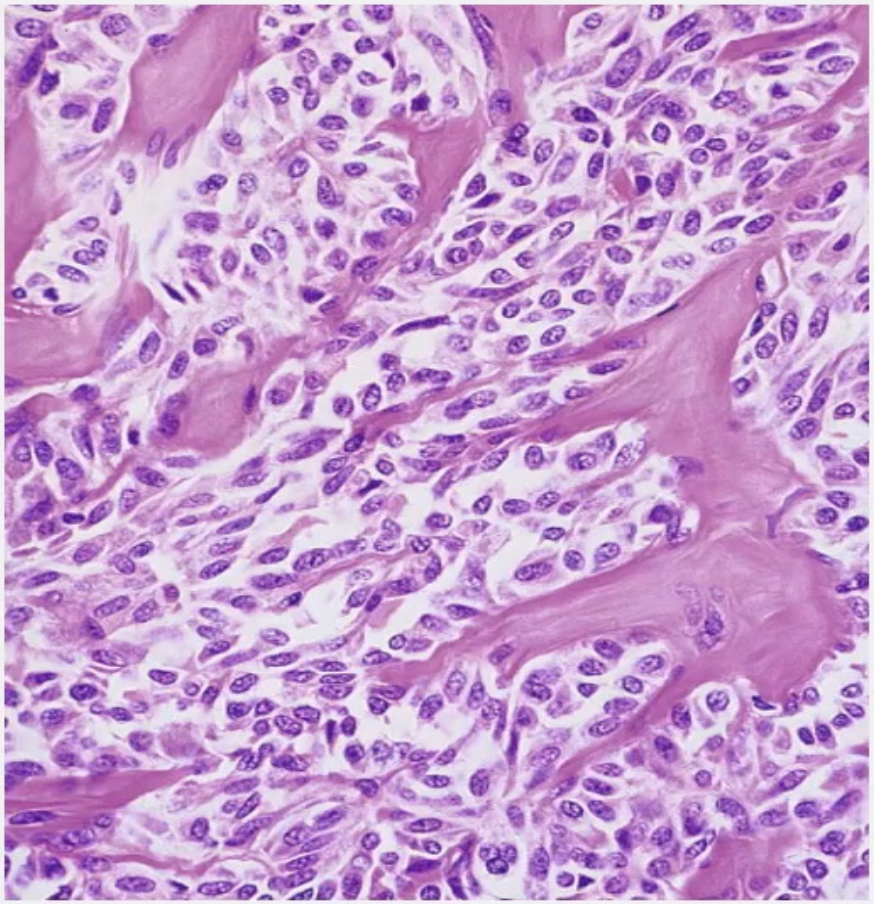

SPREAD OF THYROID CARCINOMA:

1-Direct to neck structures as recurrent laryngeal nerve producing hoarseness of voice, to larynx and trachea leading to stridor or asphyxia and to esophagus producing dysphagia.

2-Lymphatic to cervical lymph nodes. It is the main route of spread of papillary carcinoma

3-Blood spread to bone, lung and brain :occurs relatively early in follicular carcinoma but rare or very late in papillary carcinoma

PROGNOSIS: Best with papillary carcinoma

CAUSES OF SOLITARY THYROID NODULE

1-Early nodular goiter (colloid nodule) (60%). 2-Adenoma (30%). 3-Carcinoma (5%). 4-Thyroiditis (Hashimoto's and subacute) (5%).

CRETINISM (Infantile Hypothyroidism):

Aetiology: 1) Congenital thyroid hypoplasia (Sporadic Type).

2)Iodine deficiency during pregnancy (Endemic Type).

Manifestations: 1) Mental deficiency. 2)Dwarfism and hypogonadism.

3)Swollen lips and tongue.

MYXOEDEMA (Adult Hypothyroidism):

Aetiology: 1) Primary type (unknown cause, may be autoimmune).

2)Secondary due to thyroiditis, thyroidectomy, antithyroid drugs

Manifestations: Low metabolic rate + accumulation of mucopolysaccharides in tissues. The

effects are 1) Increased body weight, swollen lips, tongue and skin (nonpitting oedema)

2) Hypercholesterolaemia.