

THYROID PATHOLOGY

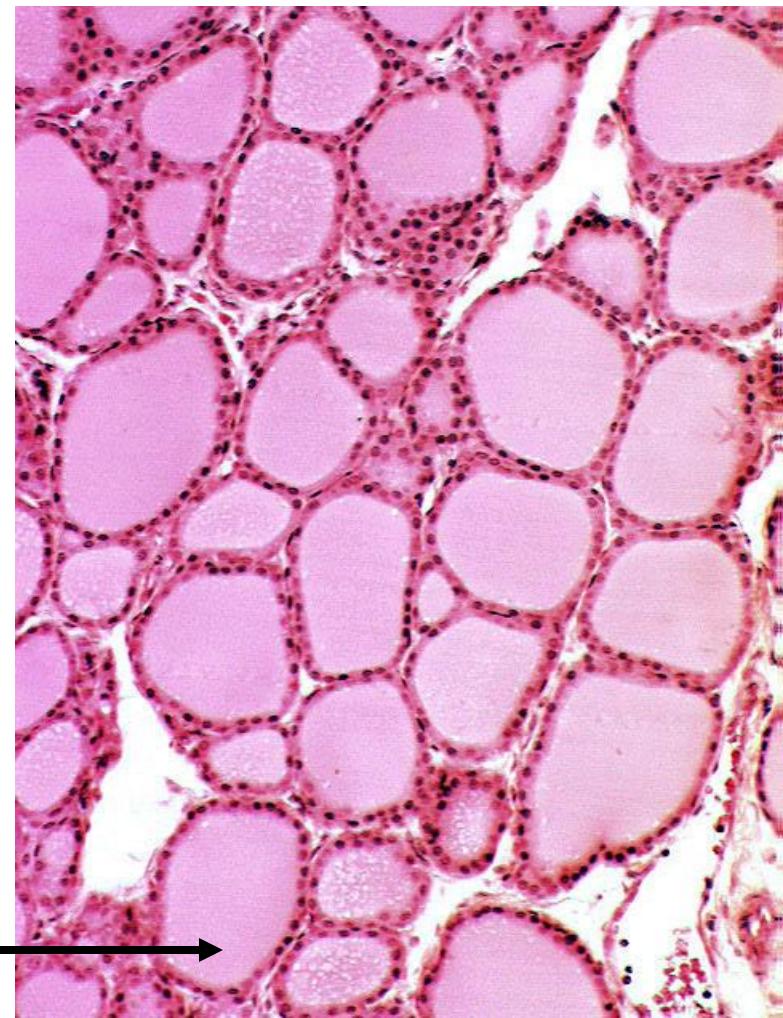
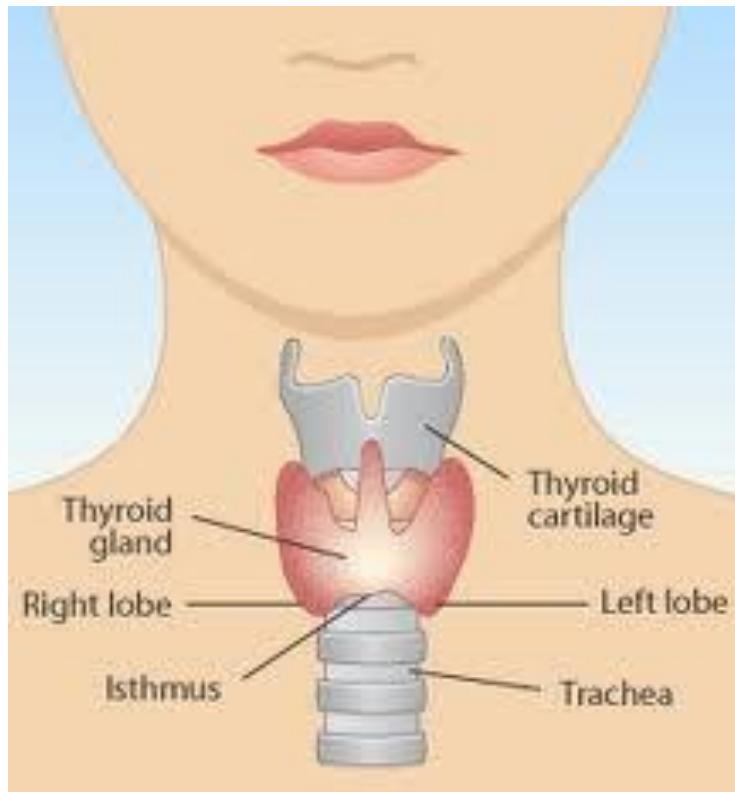
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Objectives

1. Recapitulate your knowledge on anatomy, histology and functions of the thyroid gland
2. List the causes and clinical features of hypo and hyperthyroidism
3. Describe the pathogenesis pathology of
 - Diffuse and multinodular goitre
 - Different types of thyroiditis
 - Graves' disease

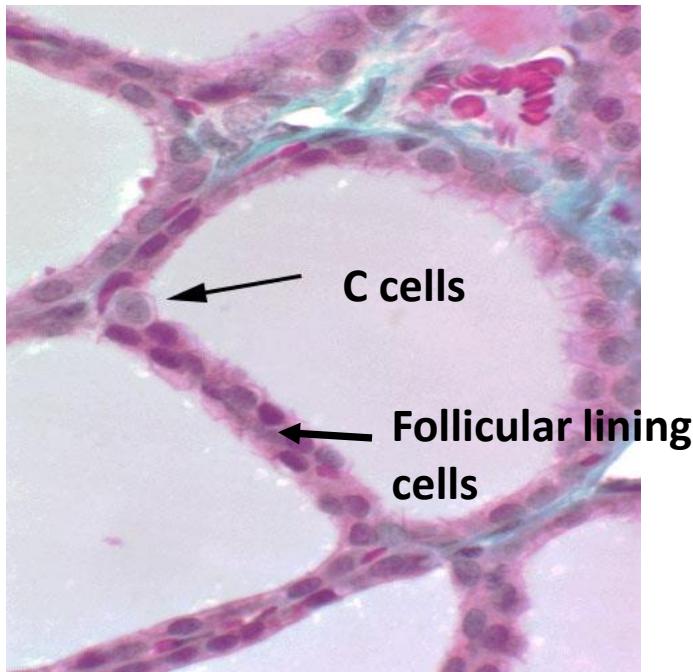
Normal thyroid gland



Colloid filled follicles

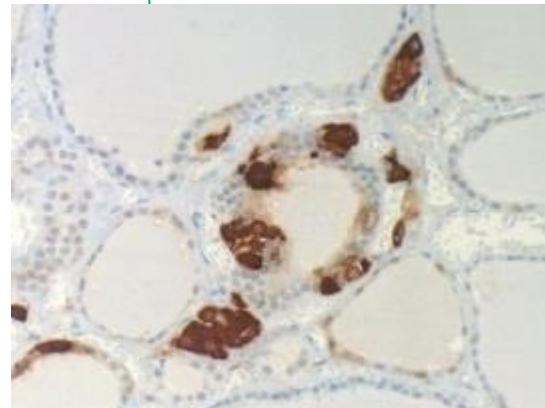
Normal thyroid Tissue

- The follicles store the colloid and are lined by cuboidal cells
- Scatters among the follicular cells are the parafollicular cells (C cells)

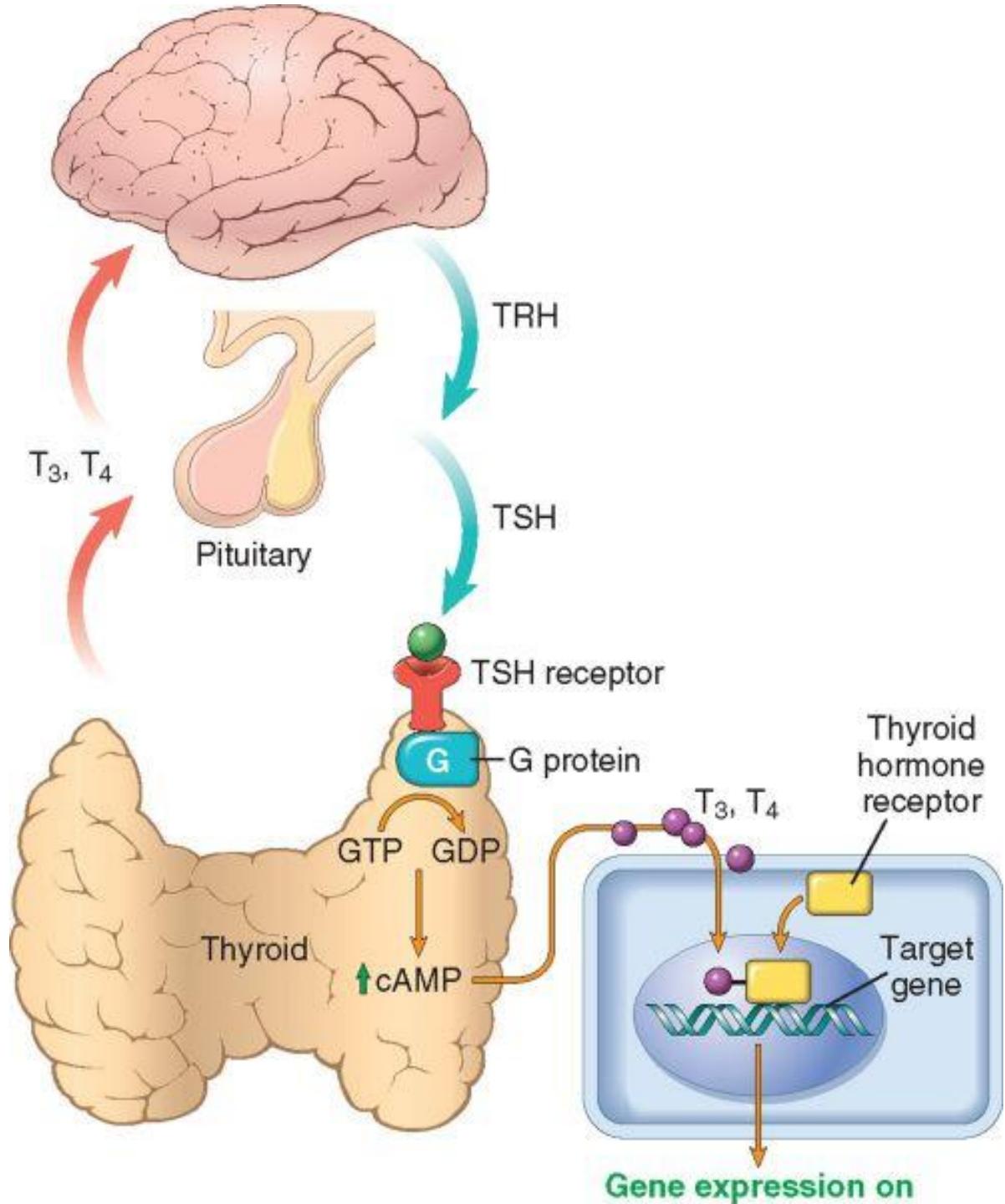


C cells

- Neuroectodermal origin
- Secretes Calcitonin
- Difficult to differentiate on H & E staining



Calcitonin
immunostaining on
normal thyroid



Disorders of thyroid gland

- Functional disorders
 - Hyperthyroidism
 - Hypothyroidism
- Thyroiditis
- Graves' disease
- Goitre
- Thyroid tumours

?Hyperthyroidism = Thyrotoxicosis

Hyperthyroidism

- Thyrotoxicosis- Hypermetabolic state caused by ↑ circulating levels of free T3 and T4
- Hyperthyroidism – Hyper function of the thyroid gland
- Thyrotoxicosis is commonly due to Hyperthyroidism
- May be due to excessive release of preformed thyroid hormone (thyroiditis)
- 1ry thyrotoxicosis - arising from an intrinsic thyroid abnormality
- 2ry thyrotoxicosis- processes outside of the thyroid

Thyrotoxicosis

ASSOCIATED WITH HYPERTHYROIDISM

Primary

- Diffuse toxic 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)

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 Features

Due to hypermetabolic state and over activity of the sympathetic nervous system

- Soft, warm, and flushed skin
- ↑Sweating
- Heat intolerance
- Weight loss
- ↑ appetite

- Cardiac manifestations
 - Tachycardia
 - Palpitations
 - Cardiomegaly
 - Arrhythmias - AF
 - Congestive heart failure
 - Reversible LV dysfunction

- Neuromuscular system
 - Tremor
 - Hyperactivity
 - Emotional lability
 - Anxiety
 - Inability to concentrate
 - Insomnia
 - Proximal muscle weakness and
↓muscle mass :thyroid myopathy



Ocular changes

- Wide staring gaze
- Lid lag are present
- True thyroid ophthalmopathy associated with proptosis is seen only in Graves disease

GIT

- Hypermotility
- Malabsorption
- Diarrhoea

Skeletal system

- Bone resorption →osteoporosis
- Atrophy of skeletal muscle

Other

- Minimal liver enlargement - fatty change
- Generalized lymphadenopathy -lymphoid hyperplasia in Graves disease

Thyroid storm

- A medical emergency - abrupt onset of severe hyperthyroidism
- Patients with underlying Graves disease
- Results from an acute elevation in catecholamine levels
- During any form of stress - infection, surgery, cessation of anti thyroid medication
- Febrile and present with tachycardia out of proportion to the fever
- Untreated - die of cardiac arrhythmias

Apathetic hyperthyroidism

- Occurring in elderly with various co-morbidities
- Unexplained weight loss/ worsening CVS disease
- Typical features of TH excess seen in younger patients are blunted.
- Diagnosis is often made during laboratory work-up for.

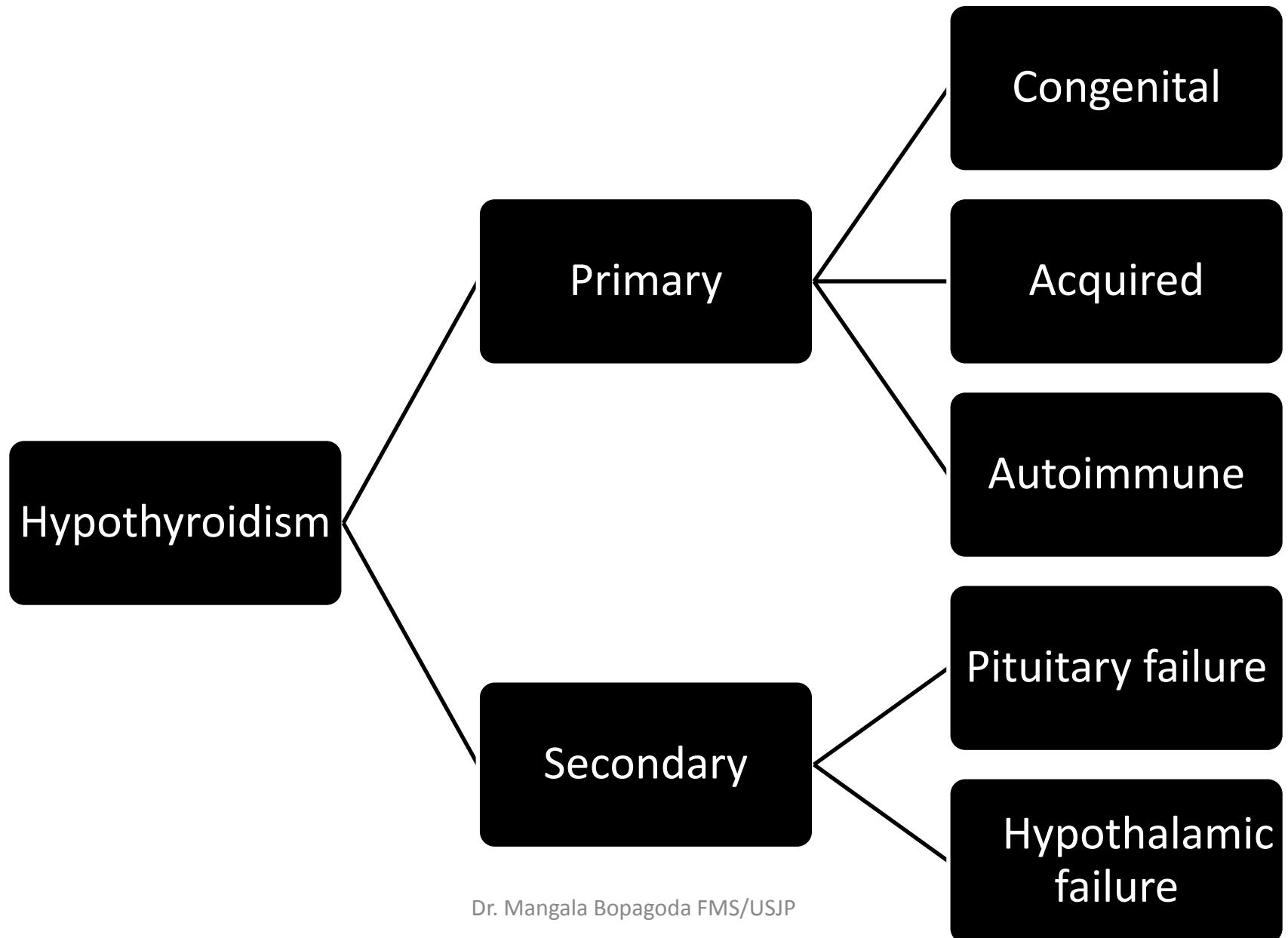
Diagnosis

- Serum TSH assays
 - Most useful single screening test
 - Sensitive TSH assays
- Free T4
- Serum T3 (T3 toxicosis)
- TRH stimulation test
- Radioactive iodine uptake

Hypothyroidism

- Common disorder
- Prevalence of overt 0.3%, subclinical > 4%
- Prevalence increases with age
- Tenfold more common in women than in men
- Can result from a defect anywhere in the hypothalamic-pituitary-thyroid axis
- Can primary or secondary
- Majority primary

Causes



Hypothyroidism

PRIMARY

- Developmental (thyroid dysgenesis)
- Thyroid hormone resistance syndrome (THRB mutations)
- Post ablative : Surgery, radioiodine therapy, or external irradiation
- Autoimmune hypothyroidism Hashimoto thyroiditis
- Iodine deficiency
- Drugs (lithium, iodides, p-aminosalicylic acid)
- Congenital biosynthetic defect (dyshormonogenetic goiter)

SECONDARY

- Pituitary failure
 - Tumor
 - Postpartum pituitary necrosis Trauma
 - Nonpituitary tumors
- Hypothalamic failure
 - Tumors
 - Trauma
 - Radiation therapy
 - Infiltrative diseases

Congenital hypothyroidism

- Majority endemic iodine deficiency
- Less common - inborn errors of thyroid metabolism (dyshormonogenetic goiter)- defects in
 - 1) Iodide transport into thyrocytes
 - 2) Iodide “organification” - binding of iodide to tyrosine residues of the storage protein, thyroglobulin
 - 3) Iodotyrosine coupling to form hormonally active T3 and T4.

Acquired hypothyroidism

- Surgical / radiation-induced ablation
- Drugs
 - Hyperthyroidism

Methimazole and propylthiouracil

- Non thyroid conditions :

Lithium, p-aminosalicylic acid

Autoimmune hypothyroidism

- Most common cause of hypothyroidism in iodine-sufficient areas of the world
- Majority Hashimoto thyroiditis
- Circulating autoantibodies
 - Anti-microsomal
 - Anti-thyroid peroxidase
 - Anti-thyroglobulin
- Can occur in isolation or in conjunction with autoimmune poly-endocrine syndrome

CRETINISM

- Hypothyroidism in infancy or early childhood
- Commonly - dietary iodine deficiency
- Rarely-Inborn errors in metabolism
- Impaired development of the skeletal system and central nervous system
 - Severe mental retardation
 - Short stature
 - Coarse facial features
 - Protruding tongue
 - Umbilical hernia
- Mental retardation is severe if maternal thyroid deficiency occur before the development of the fetal thyroid gland



MYXOEDEMA

- Hypothyroidism developing in the older child or adult
- Characterized by a slowing of physical and mental activity



- Generalized fatigue
- Apathy
- Mental sluggishness
- Slow speech
- Slow intellectual functions
- Cold intolerant
- Overweight
- constipation
- ↓sweating
- cool and pale skin
- ↑total cholesterol and low-density lipoprotein (LDL) levels
- Non-pitting edema
- Broadening and coarsening of facial features, enlargement of the tongue, and deepening of the voice.



Diagnosis

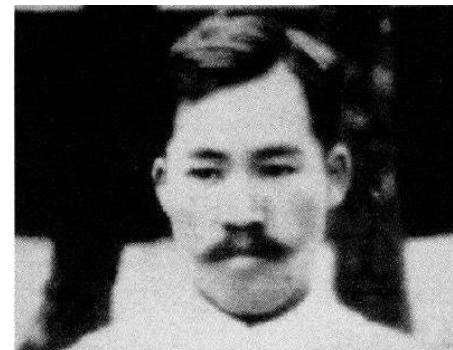
- Symptoms nonspecific
- Laboratory evaluation plays a vital role
- Unexplained weight gain,
hypercholesterolemia should be assessed
- Serum TSH level - most sensitive screening
test for this disorder.

THYROIDITIS

- Mostly due to non-infective causes
- Classified on the basis of onset and duration of disease
 - **Acute**
 - Infective or radiation induced
 - **Sub acute**
 - Granulomatous thyroiditis/ de Quervain thyroiditis
 - Acute inflammation followed by a granulomatous response
 - Self limiting
 - **Chronic**
 - Autoimmune thyroiditis
 - Reidel's thyroiditis

Chronic autoimmune thyroiditis

- Hashimoto's thyroiditis / chronic lymphocytic thyroiditis
- Morphological and immunological overlap between these entities
- Best regarded as a spectrum of a single disease
- Hashimoto described this as the first autoimmune disease of any organ in 1912.



Hashimoto Thyroiditis

- Most common cause of hypothyroidism in non endemic areas
- Disease of older women, can occur in children
- Characterized autoimmune destruction of glandular tissue gradual thyroid failure
- Most prevalent 45 - 65 years of age
- Women > men 10 : 1 to 20 : 1
- Major cause of non- endemic goiter in the pediatric population.

- Strong genetic predisposition
- Concordance of disease in 40% of monozygotic twins
- 50% of asymptomatic siblings of Hashimoto patients have circulating antithyroid Abs
- Associated with polymorphisms in multiple immune regulation genes:
 - CTLA4
 - PTPN22 polymorphisms
- Susceptibility to other autoimmune diseases(type 1 DM)

Clinical features

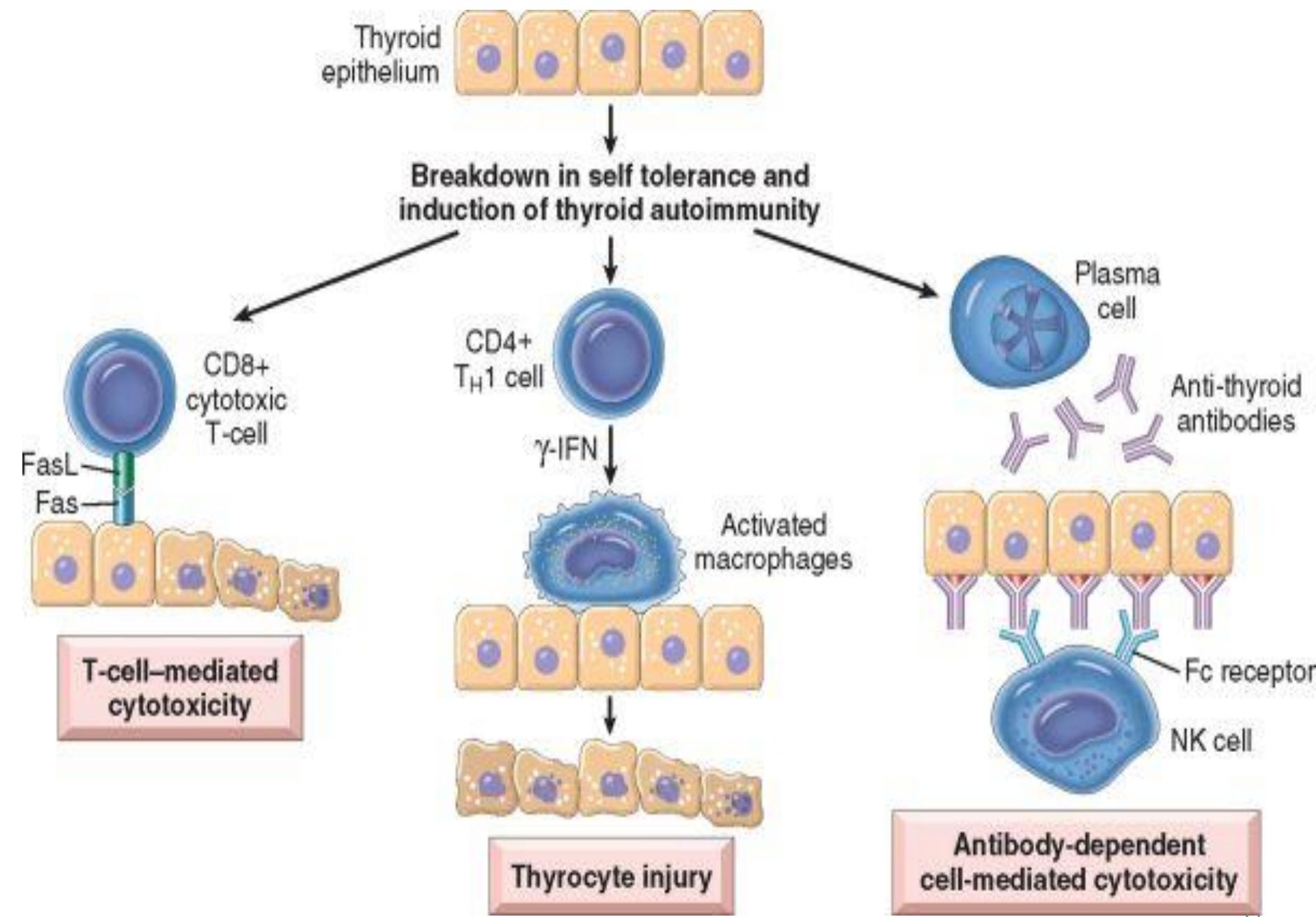
- Painless symmetric and diffuse enlargement of the thyroid
- Hypothyroidism develops gradually
- Preceded by transient thyrotoxicosis
- ↑risk for developing other autoimmune diseases, both endocrine (type 1 DM, autoimmune adrenalitis) and nonendocrine (SLE, myasthenia gravis, and Sjögren syndrome).
- ↑risk the development of B-cell NHL (MALT)
- ?Hashimoto disease and thyroid epithelial cancers

Pathogenesis of chronic autoimmune thyroiditis

- Caused by a breakdown in self-tolerance to thyroid auto-antigens.
- Autoantibodies against variety of thyroid antigens (TG and TP)
 - ↓
- Depletion of thyrocytes by apoptosis and replacement of the thyroid parenchyma by mononuclear cell infiltration and fibrosis.

Pathogenesis of chronic autoimmune thyroiditis

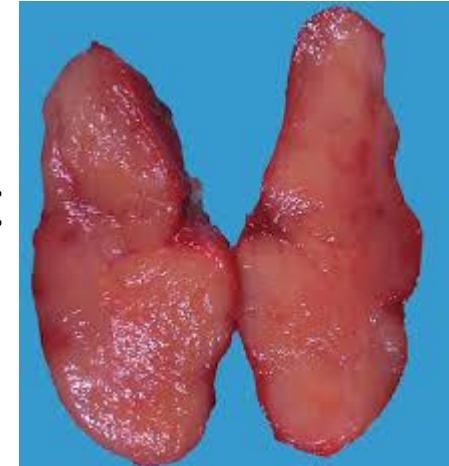
- Initiating event is sensitization of auto reactive CD4+ T-helper cells to thyroid antigens
- Multiple immunologic mechanisms contribute to thyroid follicular cell death
 1. CD8+ cytotoxic T cell–mediated cell death
 2. Cytokine - mediated cell death
 3. Antibody - dependent cell-mediated cytotoxicity (ADCC)



Pathology - Hashimoto's thyroiditis

Macroscopy

- Classic form
 - Diffuse , symmetrical firm enlargement
 - Cut surface is fleshy and lobulated



- Could be
 - Nodular enlargement
 - Solitary nodule in thyroid

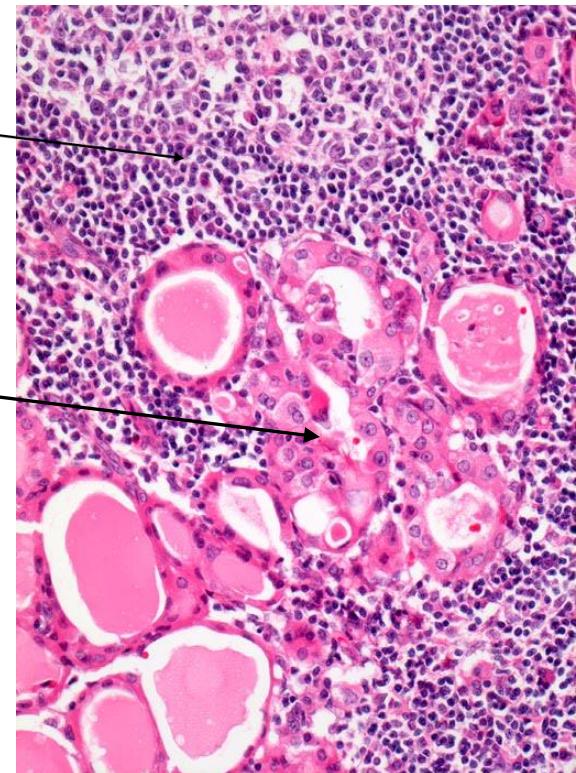
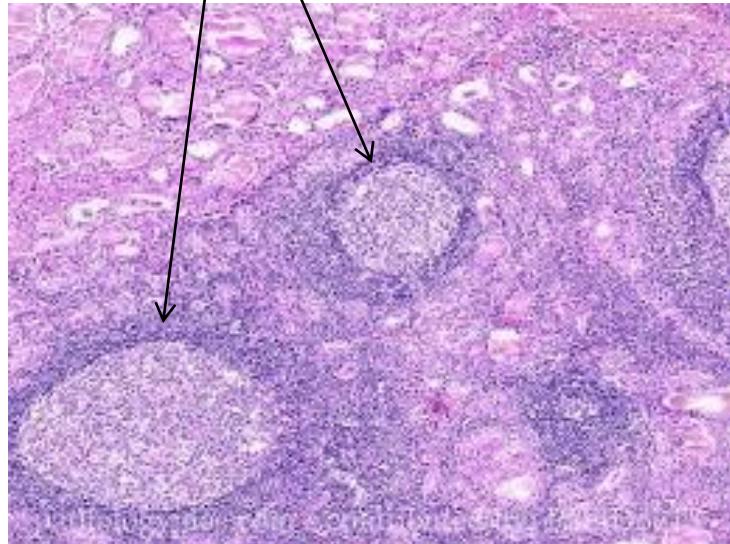


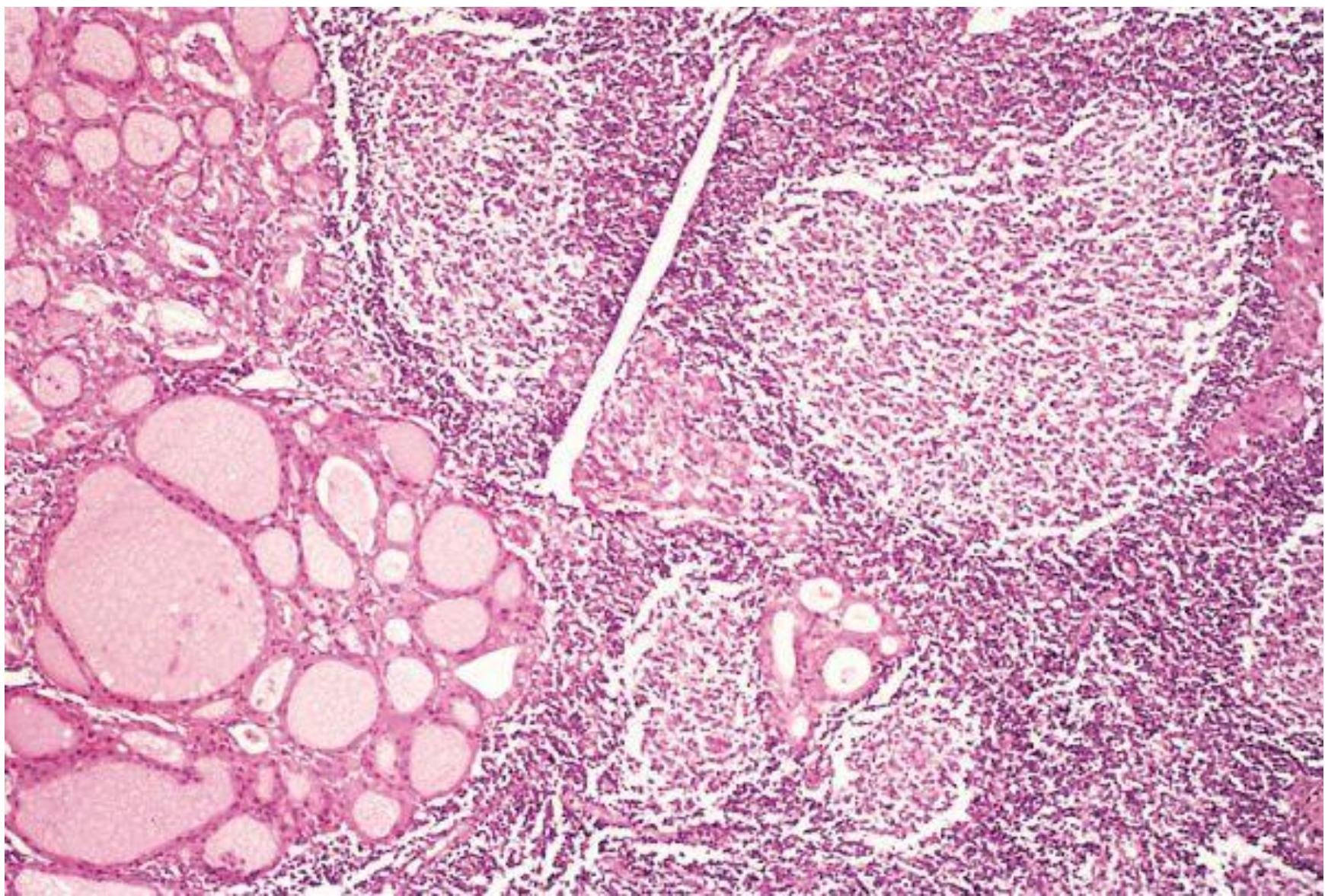
Microscopy

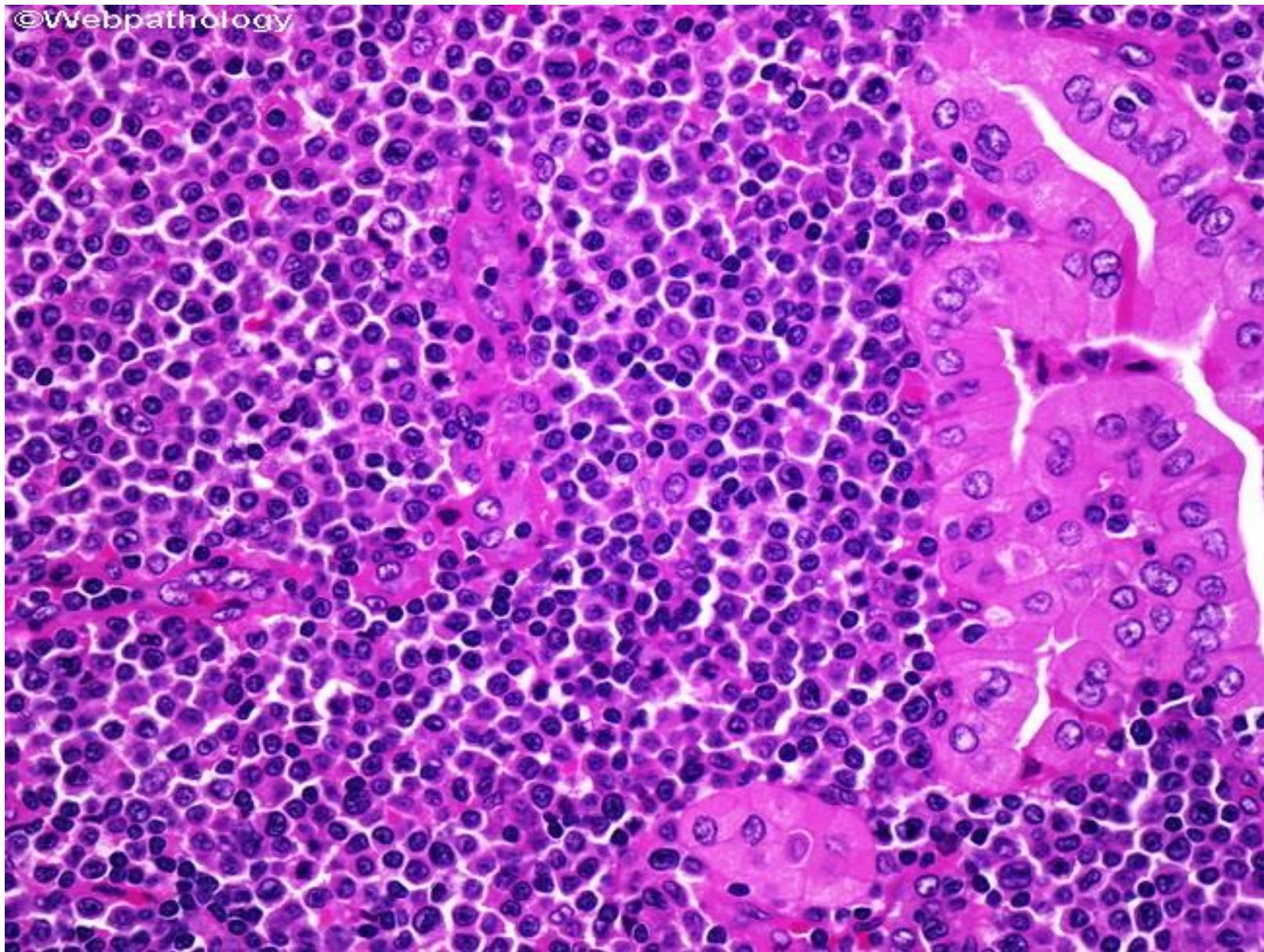
- Extensive mononuclear cell infiltration of the parenchyma : small lymphocytes, plasma cells, macrophages and well-developed germinal centers
- Follicular atrophy
- Follicular destruction
- Hürthle cell metaplasia ; abundant eosinophilic, granular cytoplasm
- Interstitial fibrosis

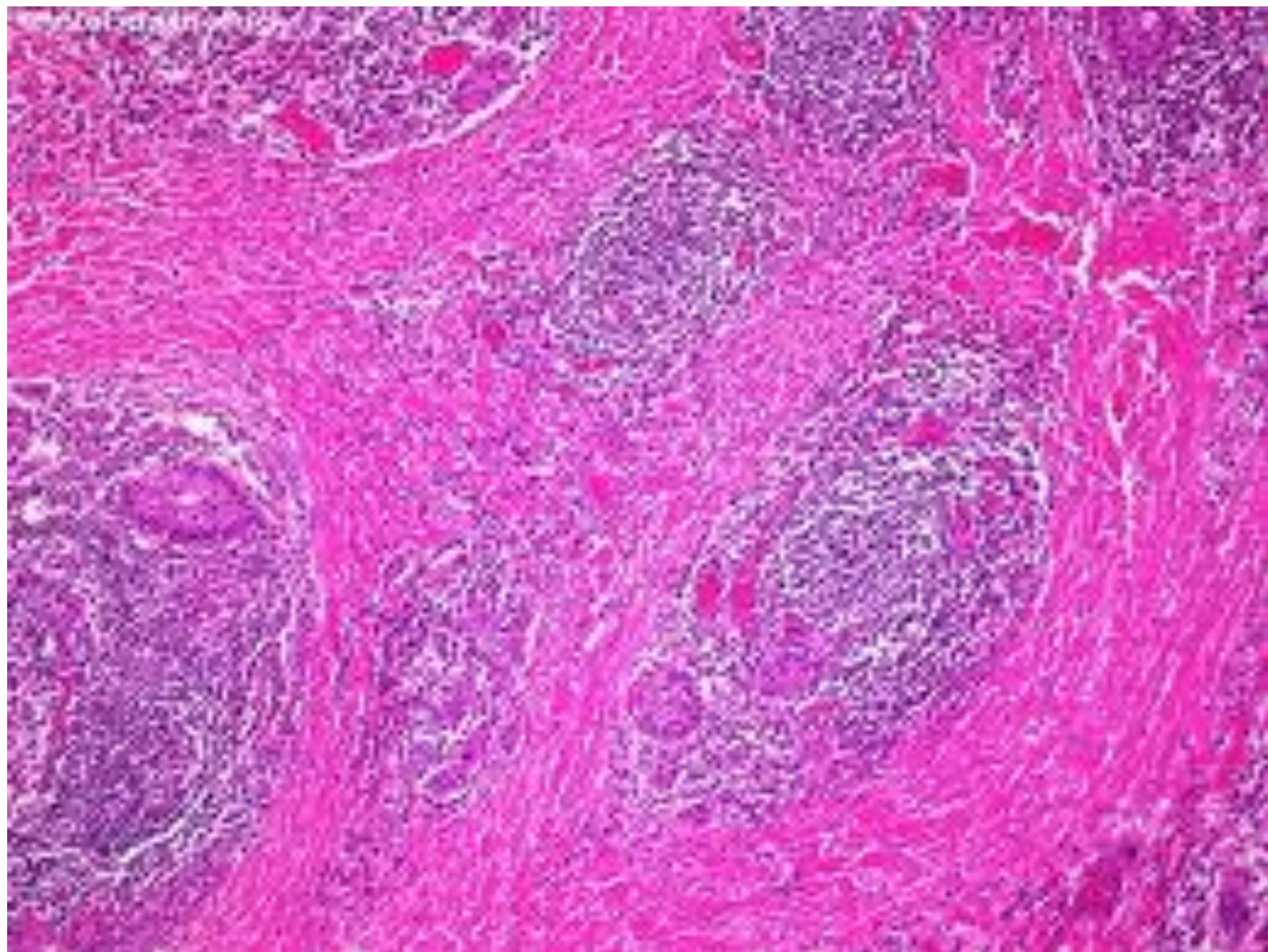
Microscopy

- Lymphocytes, plasma cells & macrophages
- Atrophic thyroid follicles
- Formation of lymphoid follicles

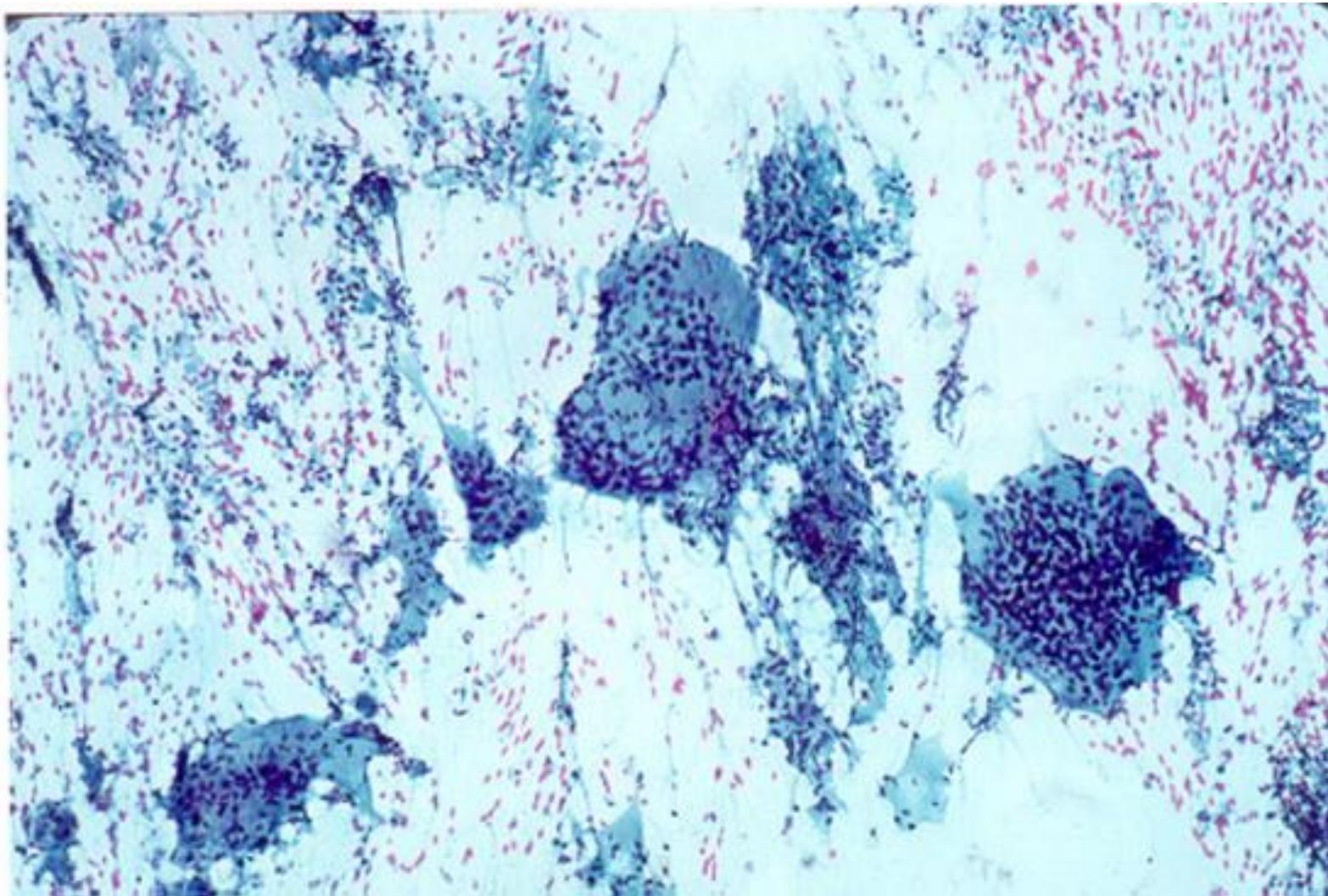








FNAC



Subacute (Granulomatous/Dequervain) Thyroiditis

- Much less frequent than Hashimoto disease
- The most common cause of thyroid pain
- Most common in ages of 40 and 50
- Women : men ratio is 4 : 1

Clinical features

- Thyroid pain
- Majority have history of an URTI
- Variable enlargement of the thyroid
- Nearly all patients have transient hyperthyroidism
- RI uptake is diminished
- After recovery, generally in 6 to 8 weeks, normal thyroid function returns

Pathogenesis of subacute thyroiditis

- ?Triggered by a viral infection
- Majority of patients have a history of an URTI just before the onset of thyroiditis
- Seasonal incidence - peak in the summer
- Clustering of cases in association with coxsackievirus, mumps, measles, adenovirus
- Immune response is virus-initiated and not self-perpetuating, so the process is limited.

Pathology - subacute thyroiditis

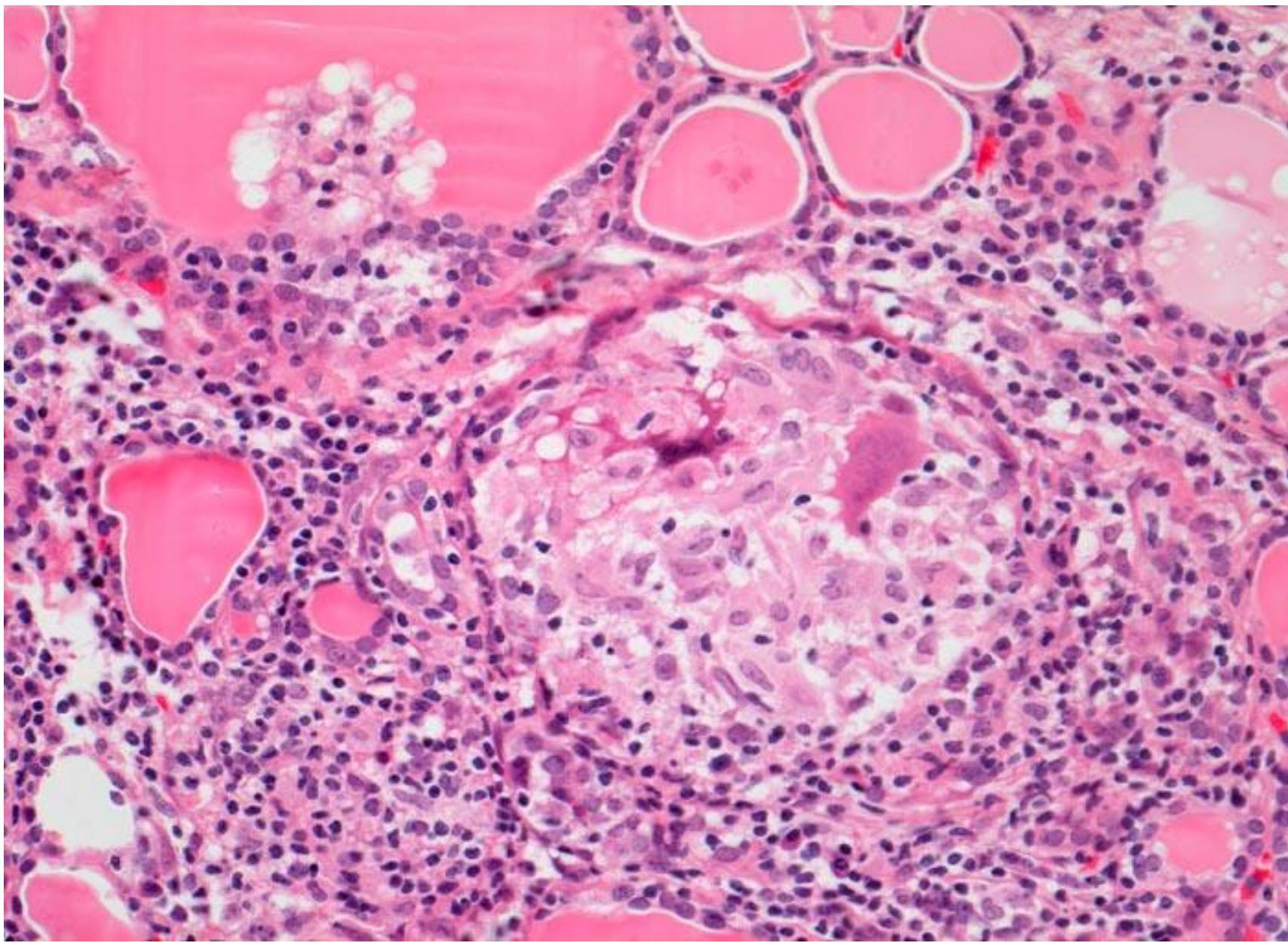
Macroscopy

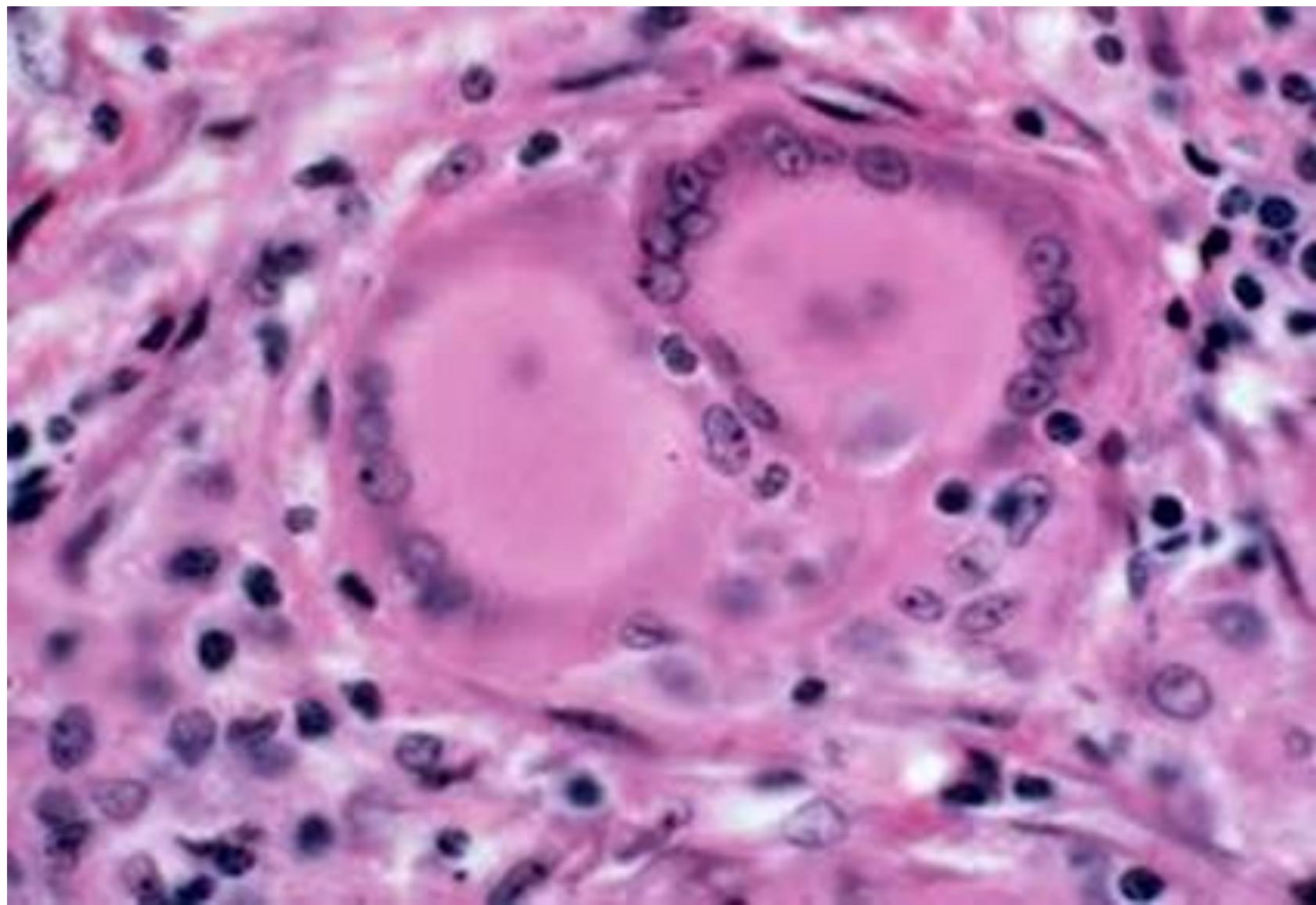
- Enlarged
(unilateral/ bilateral)
- Firm
- Intact capsule
- Slightly adherent to surrounding structures
- C/S Firm and yellow-white involved areas stand out from the more rubbery, normal brown thyroid substance.

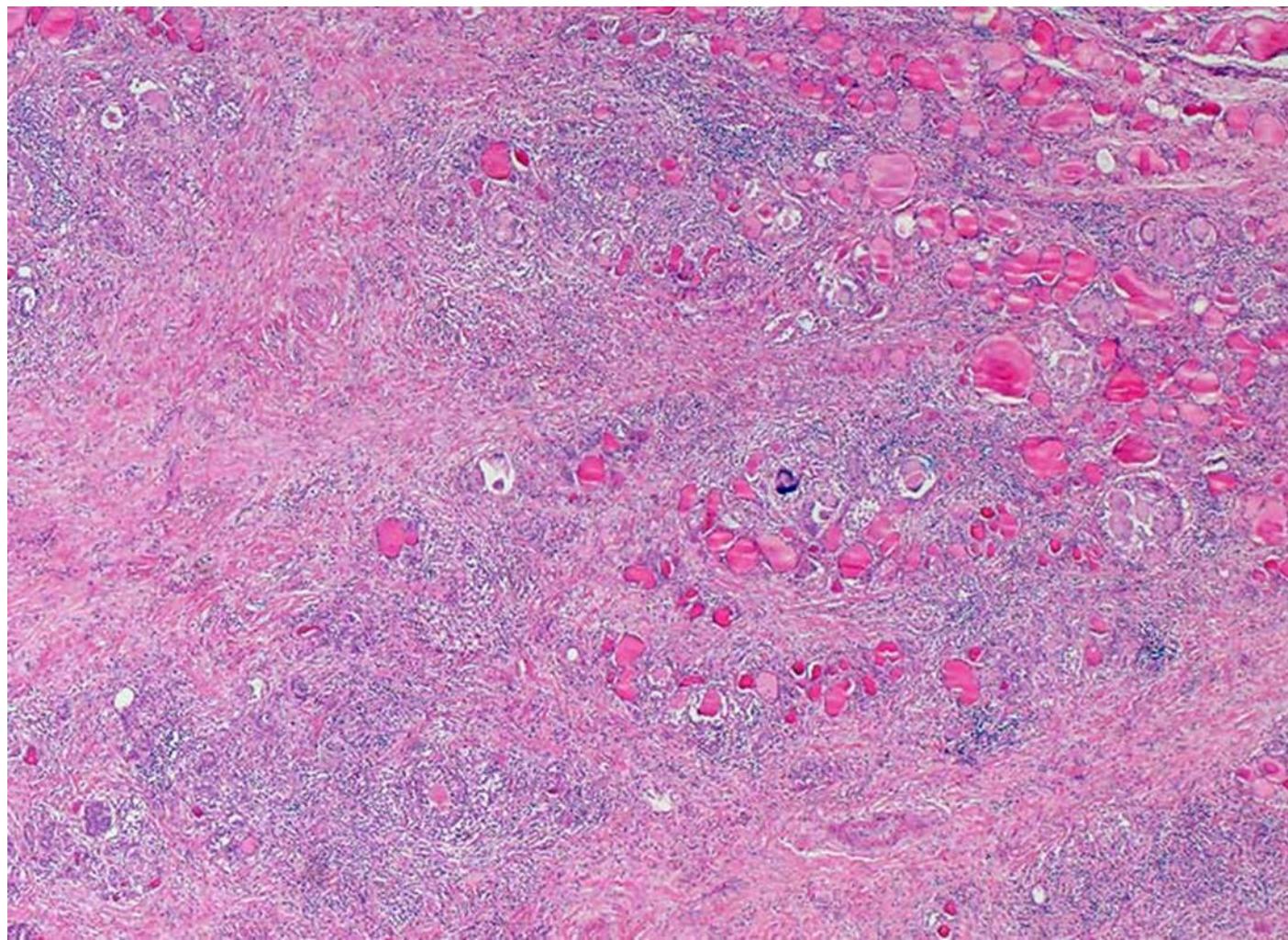


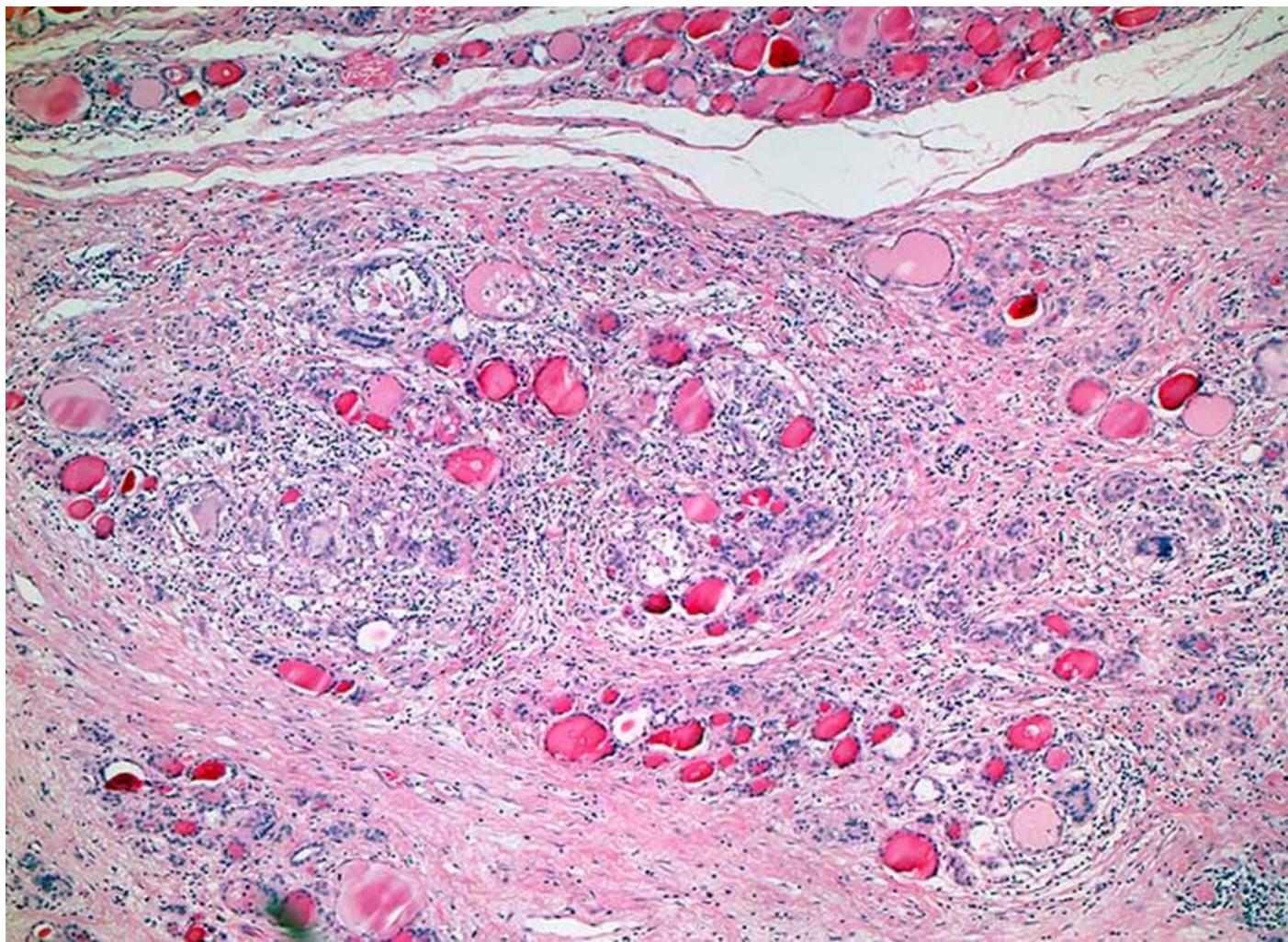
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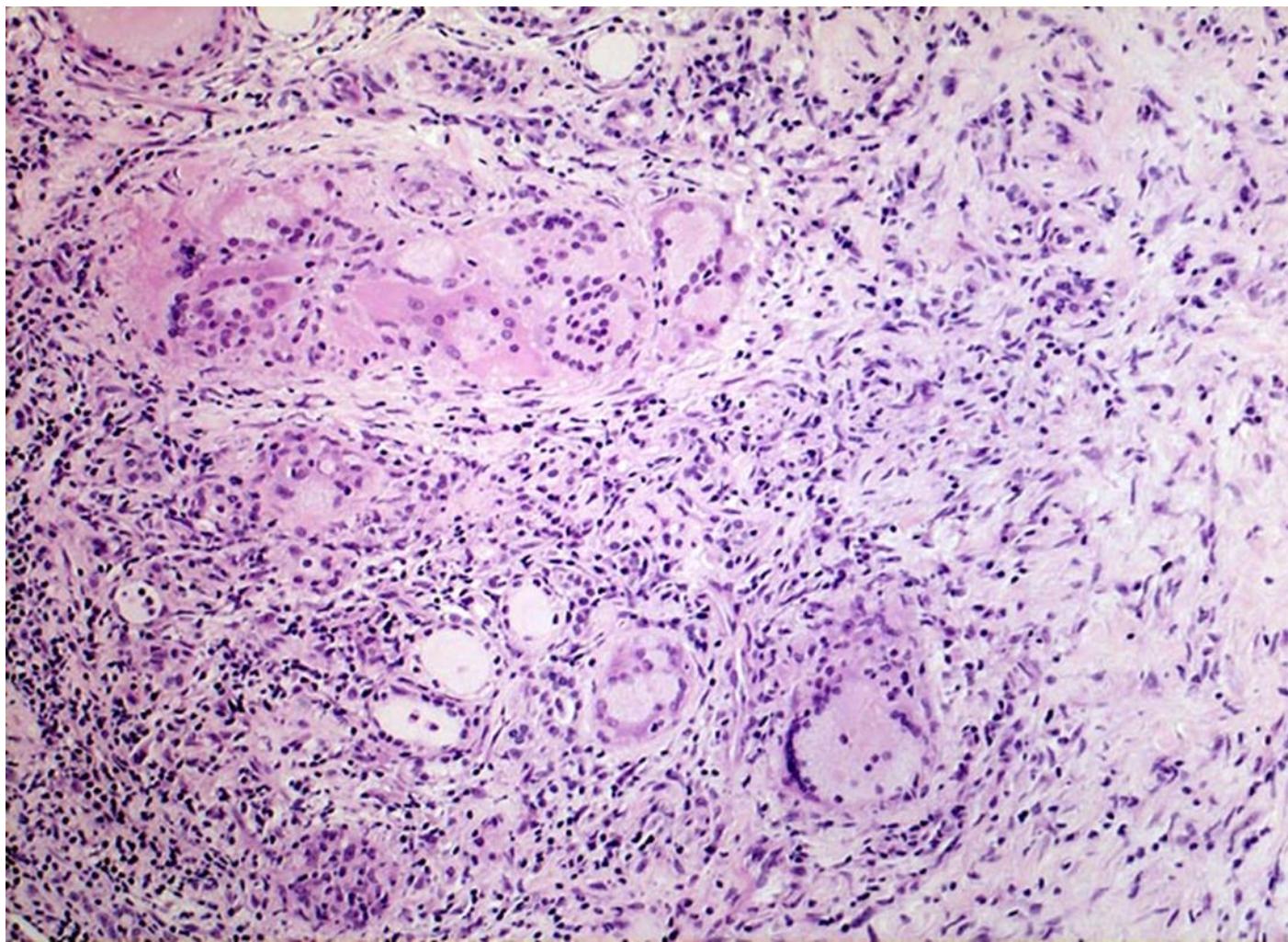
- Changes are patchy and depend on the stage of the disease.
- ***Acute*** : Entirely disrupted scattered follicles replaced by neutrophils forming microabscesses
- ***Subacute***: Damaged thyroid follicles surrounded by aggregates of lymphocytes, activated macrophages, and plasma cells
- Multinucleate giant cells enclose pools or fragments of colloid
- ***Chronic*** : Chronic inflammatory infiltrate and fibrosis replace the foci of injury
- Different histologic stages may found in the same gland







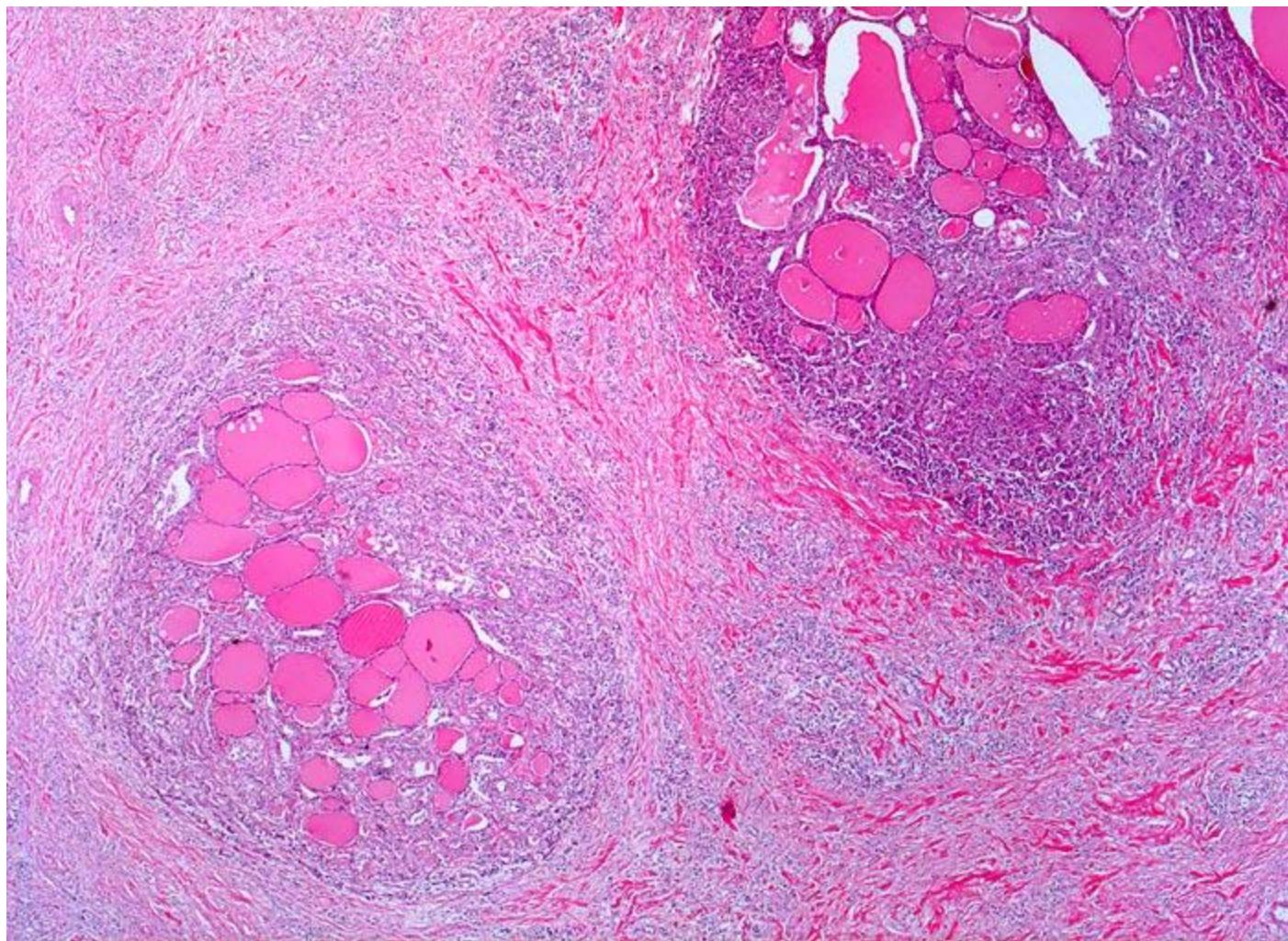


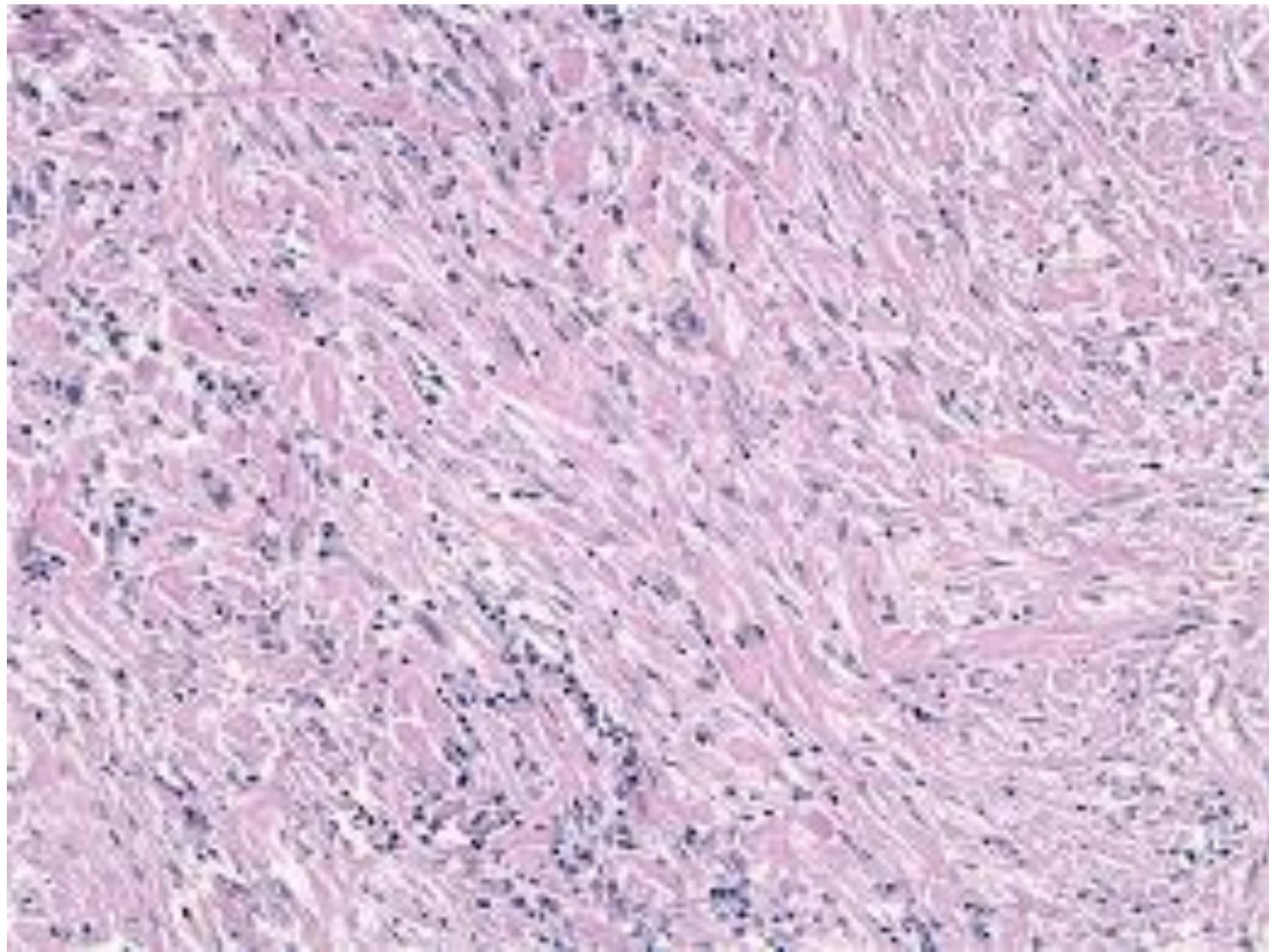


Riedel thyroiditis

- A rare disorder of unknown etiology
- Presence of circulating anti-thyroid Abs in most patients -? autoimmune etiology
- Extensive fibrosis involving the thyroid and contiguous neck structures
- Hard and fixed thyroid mass
- Associated with idiopathic fibrosis in other sites in the body-retroperitoneum







Graves' Disease

- Also known as diffuse toxic goitre
- Another autoimmune thyroid disease
- Characterized by
 - Hyperthyroidism -diffuse hyperfunctional thyroid enlargement
 - Eye changes
 - Pretibial myxedema
- Can be associated with autoimmune diseases of other organs.
- Auto-antibodies are directed against thyroid antigens.

Graves' Disease

- Most common cause of endogenous hyperthyroidism
- Peak incidence between 20 - 40 years of age.
- Women : men ratio 10: 1
- Genetic factors are important
 - 30% to 40%, in monozygotic twins
 - < 5% among dizygotic
- linked to polymorphisms in immune-function genes like CTLA4 and PTPN22 and the HLA-DR3 allele

Pathogenesis

- Due to breakdown in self-tolerance to thyroid auto-antigens - TSH receptor.
- Production of multiple autoantibodies

Antibodies associated with Graves' disease

- Thyroid- stimulating immunoglobins (TSI)
 - Binds to TSH receptor-increase release of thyroid hormones
 - Relatively specific
- Thyroid growth-stimulating immunoglobins(TGI)
 - Stimulate proliferation of thyroid epithelium
- TSH binding inhibitor immunoglobins(TBII)
 - Inhibitory to binding of TSH to its own receptors
 - Depending upon its action as inhibitory or stimulatory to follicular epithelium gets episodes of hyper or hypo thyroidism

Ophthalmopathy

- Characteristic of Graves disease
- ↑volume of the retro-orbital connective tissues and extraocular muscles
 - (1) Infiltration of the retro-orbital space by mononuclear cells
 - (2) Inflammatory edema and swelling of extraocular muscles
 - (3) ↑extracellular matrix components
 - (4) Fatty infiltration

Pathology of Graves disease

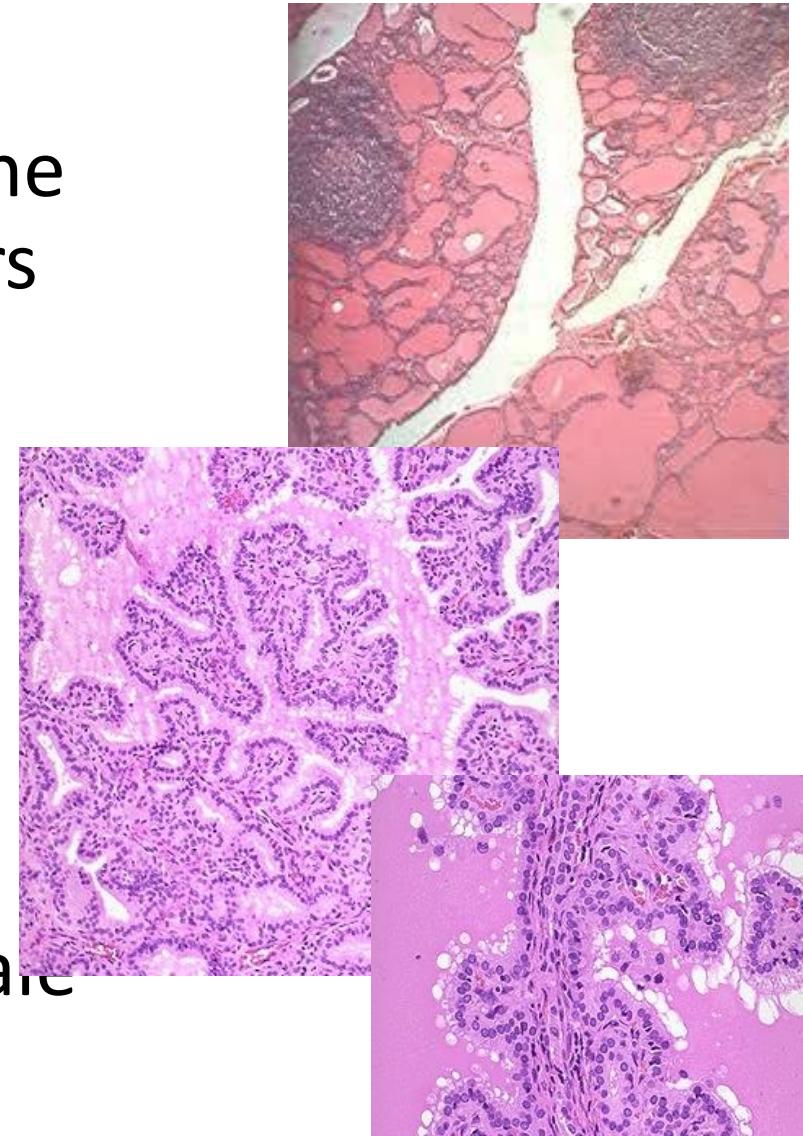
Macroscopy

- Diffuse and Symmetrically enlarged gland
- Increases in weight to (> 80 gm)
- Cut surface is red- brown due to vascularity
- Fleshy and homogenous

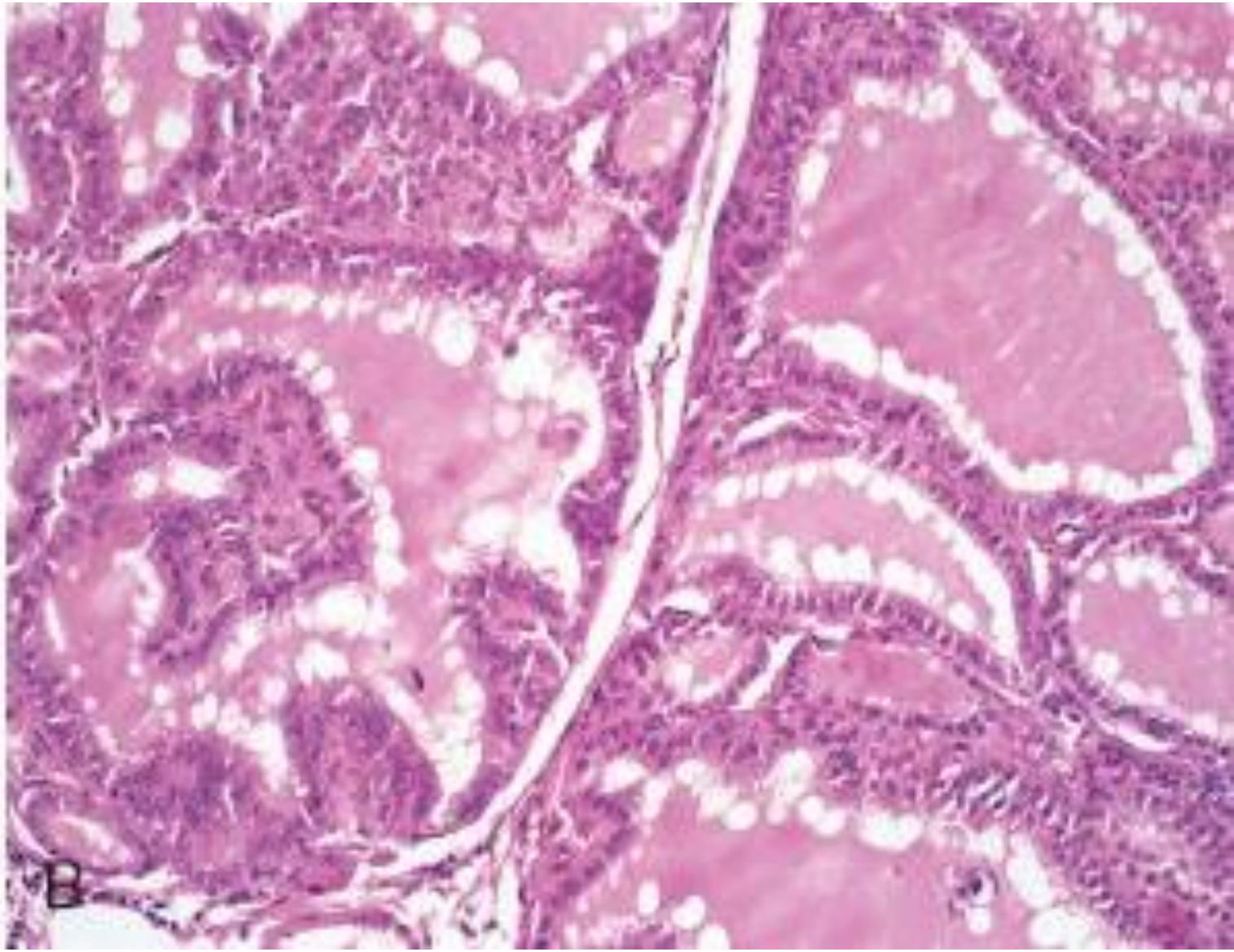


Microscopy

- Increased vascularity
- Lymphocytic infiltration of the stroma with germinal centers
- Epithelial hyperplasia and hypertrophy
- The follicles are lined by tall columnar epithelium and heaped up into papillary infoldings
- Colloid is markedly scanty, pale
- Colloid resorption



The morphology changes widely because of effective medical therapy



Clinical features

- Diffuse enlargement of the thyroid
- Audible “bruit.”
- Wide, staring gaze and lid lag
- The ophthalmopathy - exophthalmos
- Infiltrative dermopathy /pretibial myxedema - scaly thickening and induration skin overlying the shins
- ↑Risk for other autoimmune diseases-SLE pernicious anemia, type 1 DM, Addison disease.

Goitre

- The term goitre is used in general to describe an enlargement of thyroid gland.
- Goitre is defined as thyroid enlargement due to compensatory hypertrophy & hyperplasia of the follicular epithelium in response to thyroid hormone deficiency.
- The end result is generally euthyroid state , but at various stages hyperthyroidism and hypothyroidism can result.

Goitre

- 2 morphological forms
 - diffuse non-toxic goitre (simple/colloid goitre)
 - Diffuse enlargement of thyroid gland unaccompanied by hyperthyroidism
 - Try to maintain euthyroid state through stages of hypothyroidism
 - Could be
 - Endemic
 - sporadic
 - Nodular goitre (multinodular goiter/adenomatous goitre)
 - End stage of long standing simple goitre
 - Tumour like enlargement
 - Could give rise to hyperthyroidism

Pathogenesis of simple & multinodular goitre

Iodine lack



Deficiency of thyroid
hormone production



goitrogens

Excess TSH stimulation



Cyclic hyperplasia and involution of thyroid gland



Diffuse goitre

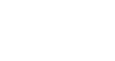


Repeated hyperplasia and involution of thyroid gland

Growth of
hyperplastic areas



Fibrosis of
involved
areas



Nodular goitre



Diffuse goitre

- Moderate enlargement of the gland
- Symmetrical and diffuse
- Microscopically
 - in hyperplastic stage
 - Tall columnar epithelium forming papillary infoldings
 - In involution stage
 - Flattened cells lining large follicles



Multinodular goitre

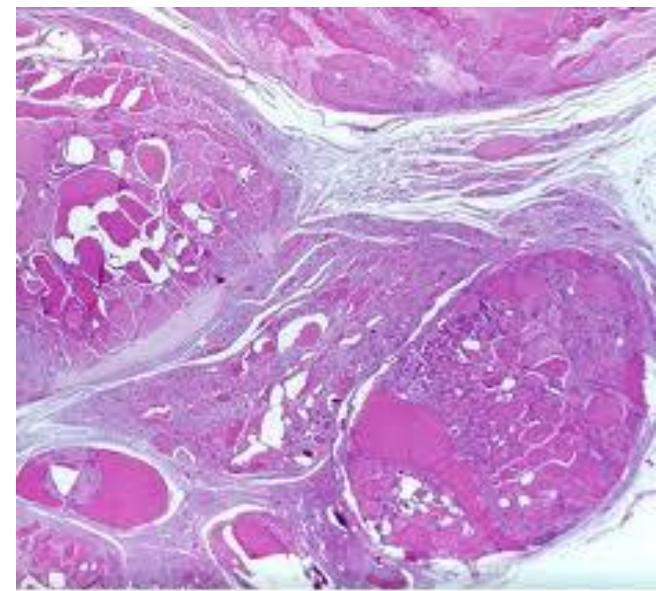
Macroscopy



- Asymmetrical enlargement
- Nodularity
- Fibrous scarring
- Haemorrhage
- Calcification
- Cystic degeneration

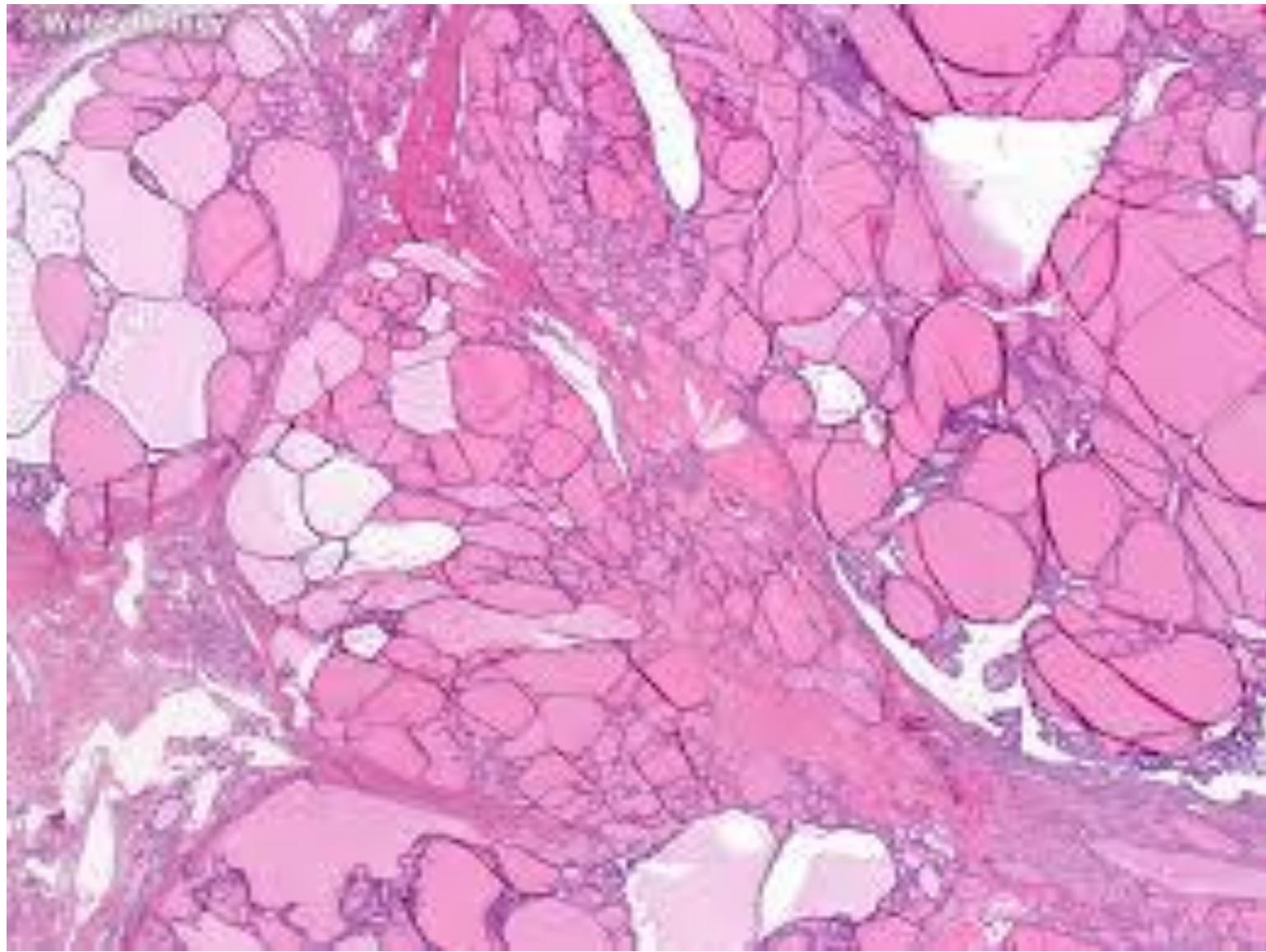
Microscopy

- Nodule formation
- Follicles of varying size
- Haemorrhage
- Fibrosis
- Calcification
- Cystic change











Neoplasms of the Thyroid

Thyroid tumours- general facts

- All thyroid tumours are common in females than in men.
- Usually present as a solitary nodule.
- Majority of clinically detected solitary nodules are a dominant nodule of a multinodular goitre
- Tumours are ‘cold’ on thyroid scan.
- Benign tumours are commoner than the malignant.
- In young age and in men, a solitary nodule is regarded with more suspicion than in a middle aged women.

Thyroid tumours-Read on

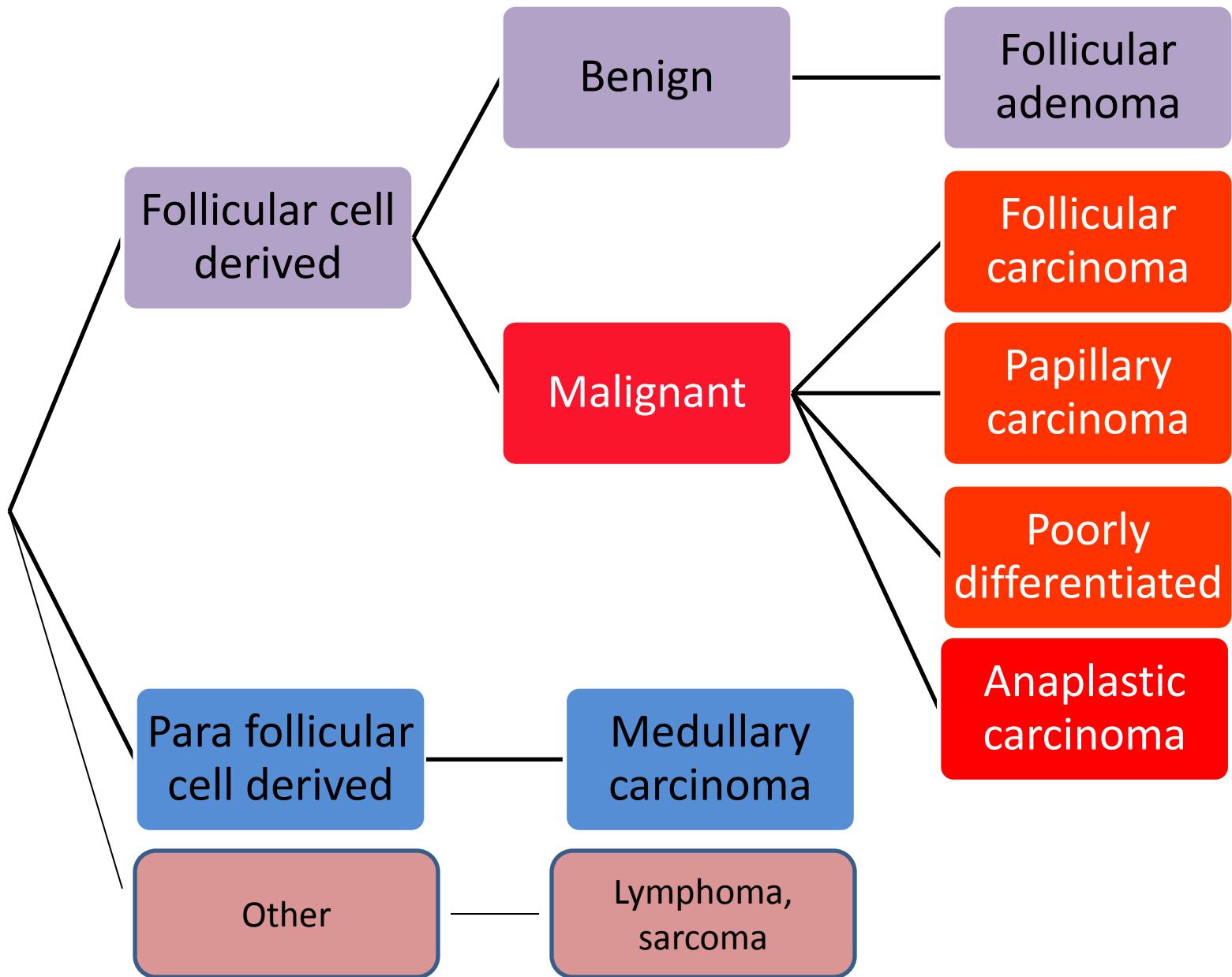
- Epidemiology of thyroid tumours
- Risk factors
- Radiation and thyroid cancers
- Molecular genetics in thyroid cancer
- Prognostic factors in thyroid cancer

Features favour neoplastic nodule

- Solitary nodules
- Younger patients
- Males
- History of radiation treatment to the head and neck region
- Cold nodules

Thyroid tumours -classification

Thyroid
tumours



Follicular adenoma

- Commonest of all thyroid tumours
- Rarely can cause hyperthyroidism -‘toxic adenoma’
- Encapsulated and compress the surrounding thyroid tissue
- No invasion of the capsule is the key difference from follicular carcinoma
- Not the precursors of follicular carcinoma

Pathology

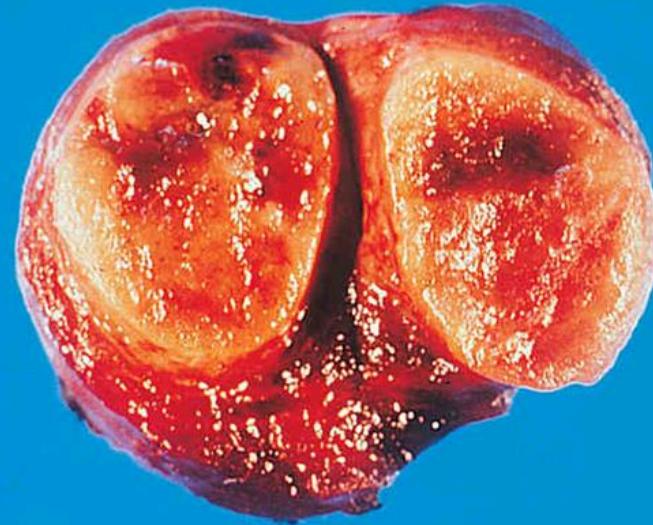
Macroscopy

- Solitary
- Spherical
- Encapsulated
- Well demarcated from surrounding thyroid
- Average 3 cm in diameter (some larger ≥ 10 cm)
- Cut surface bulges
- Color : gray-white to red-brown
- Areas of hemorrhage, fibrosis, calcification, and cystic change +





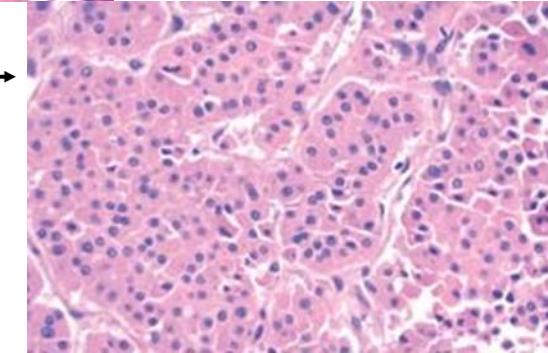
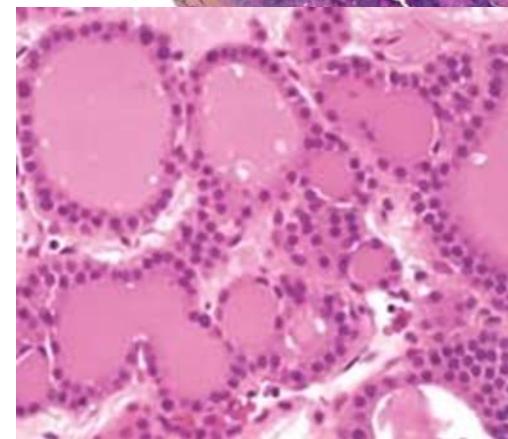
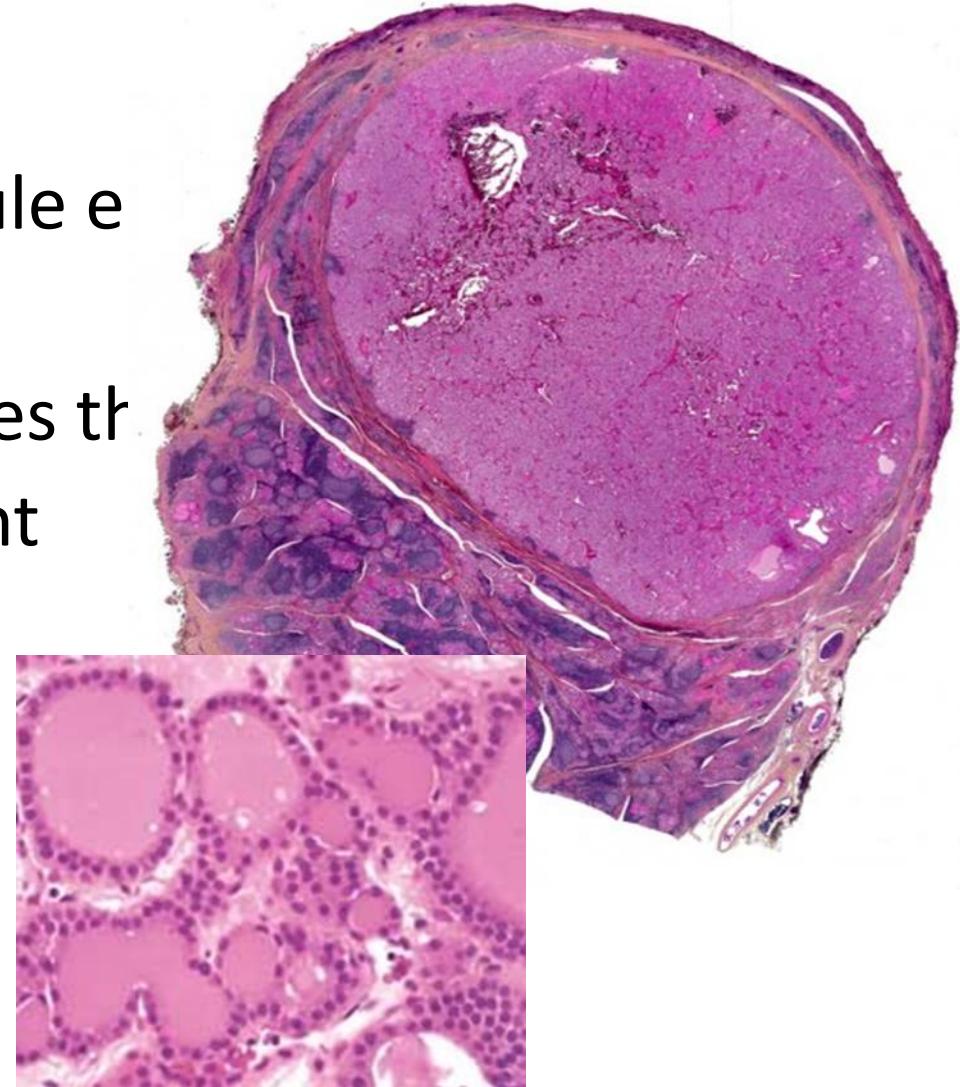
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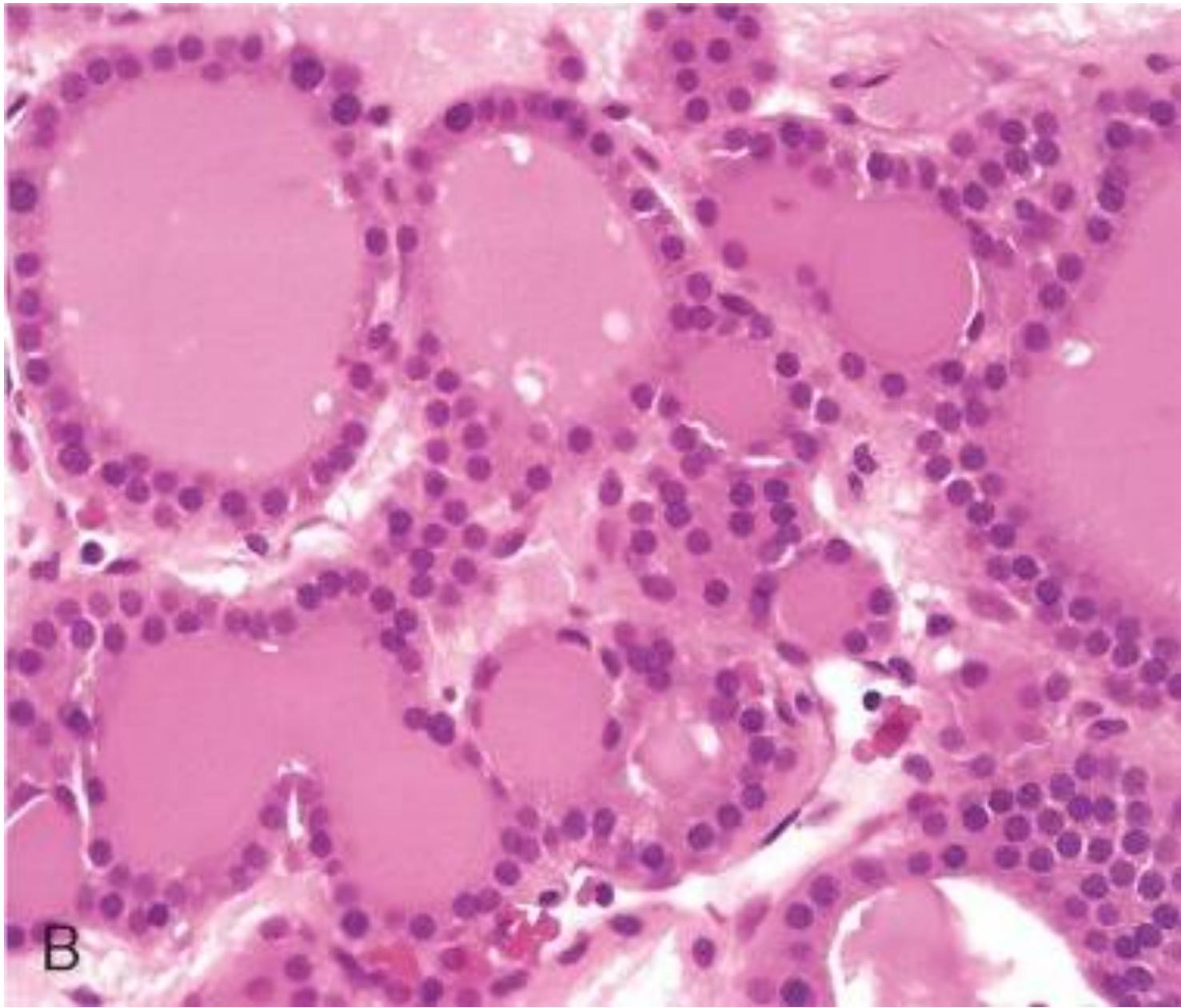


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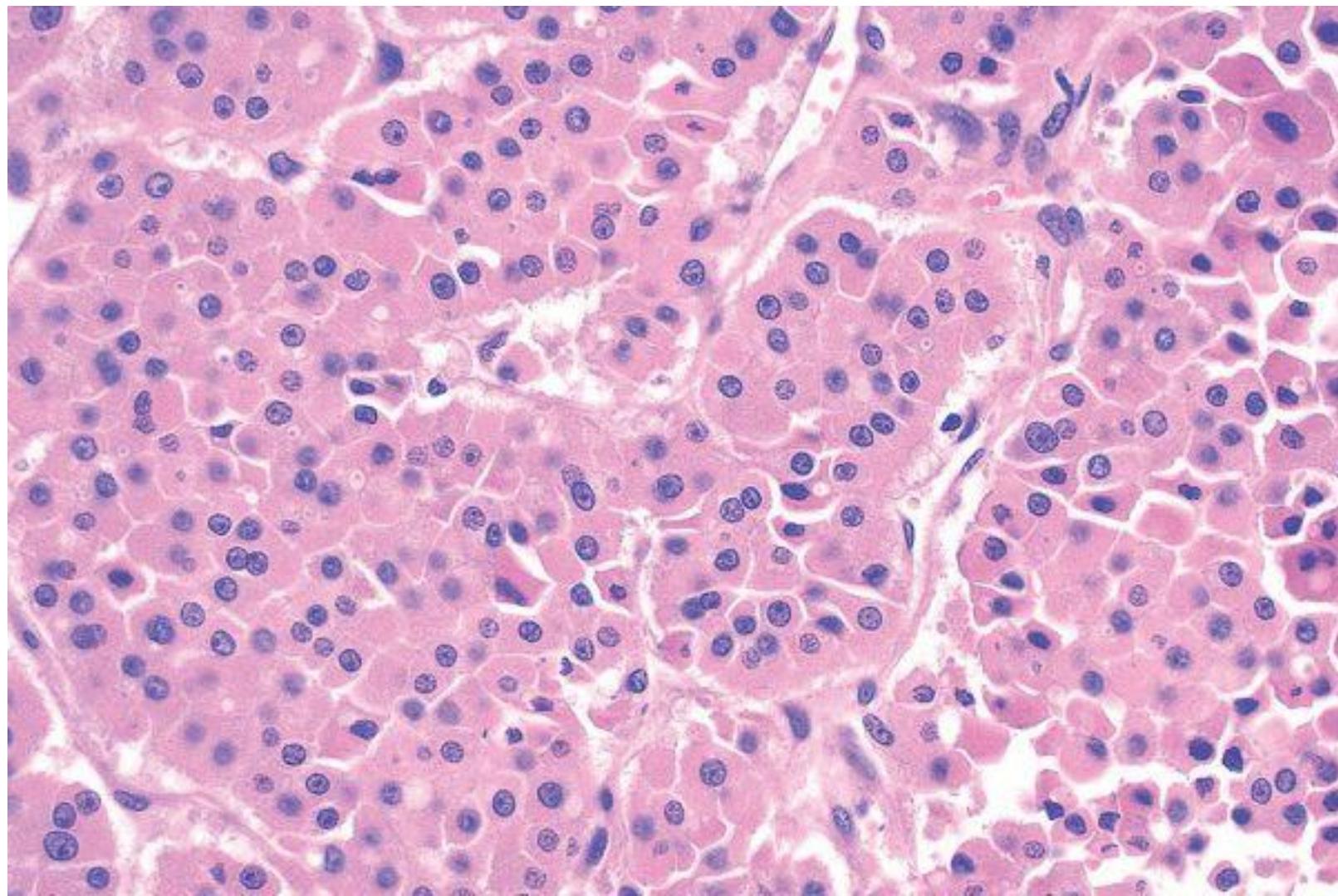
Microscopy

- Well-formed intact capsule e
- Follicular growth pattern
- Uniform-appearing follicles th
- Distinct from the adjacent non-neoplastic thyroid
- Follicular epithelial cells little variation in cell and nuclear morphology
- Mitotic figures are rare
- Occasionally Hürthle cell change →
- No capsular and/or vascular invasion





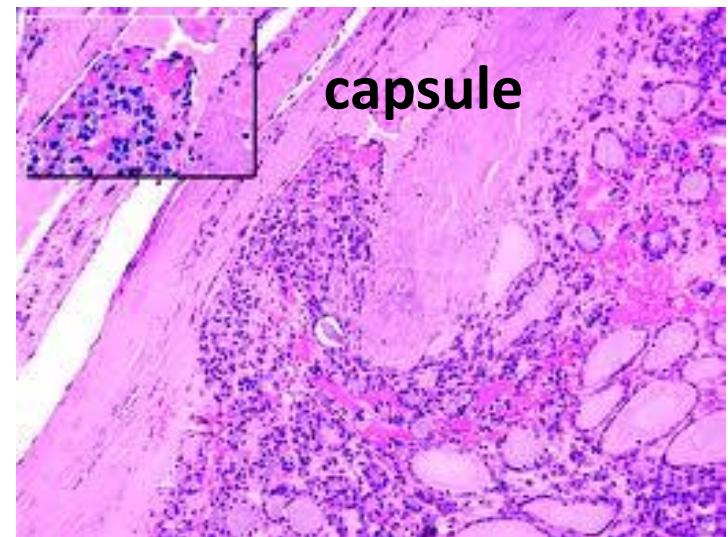
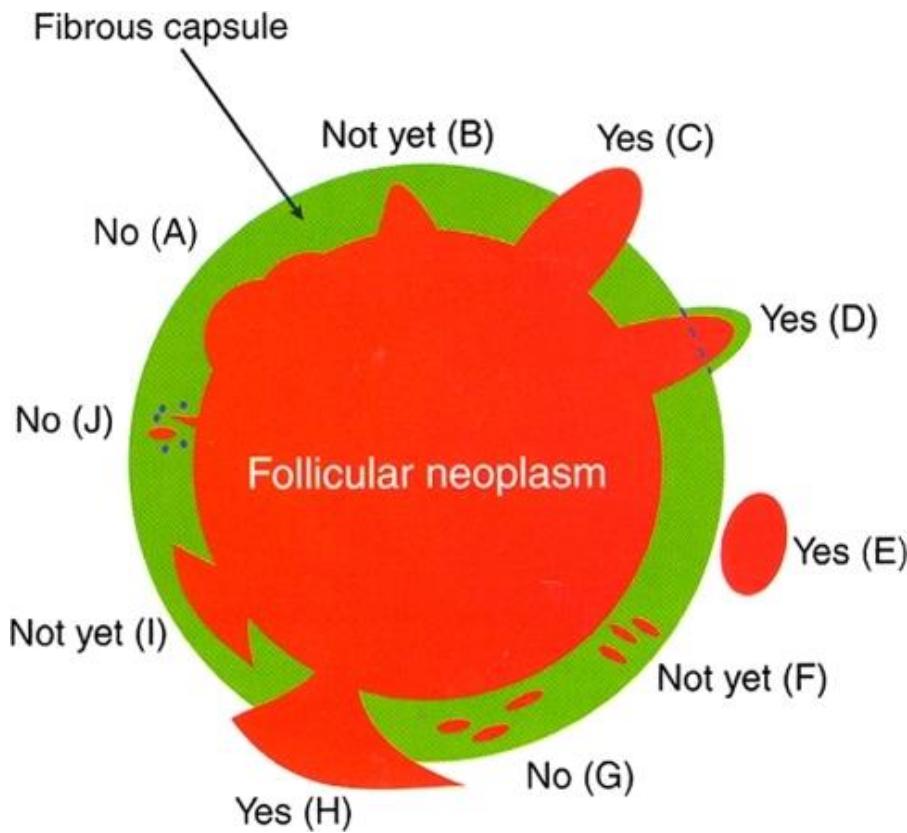
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- Extensive mitotic activity
- Necrosis
- High cellularity warrants careful examination of the capsule and the nuclear features

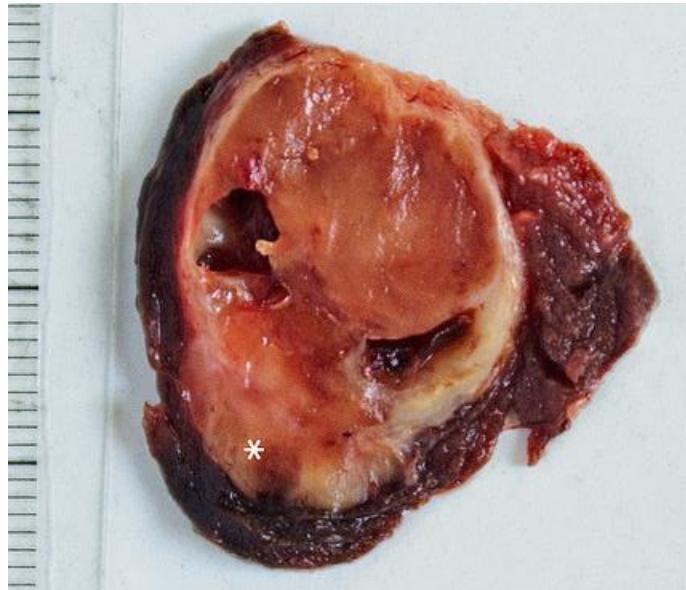
Follicular carcinoma

- These are also composed of small /large follicles
- Essential feature is infiltration across its capsule or invasion of the vessels.



Follicular carcinoma

Minimally invasive

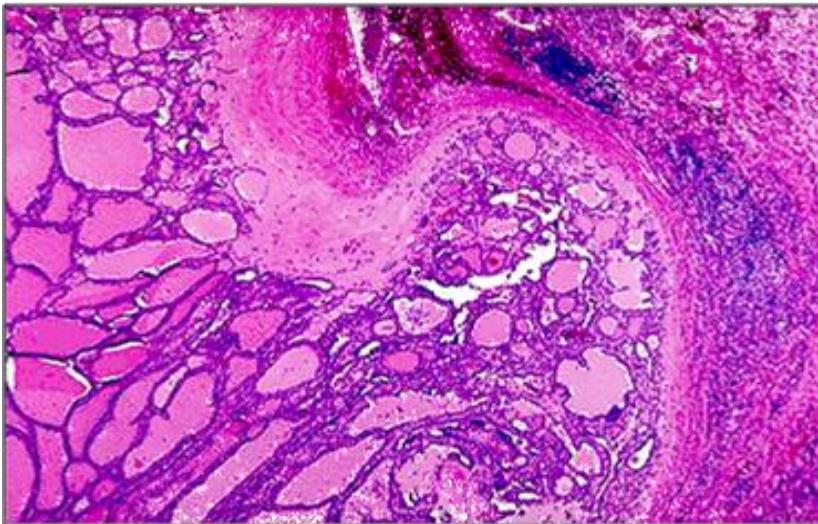


Widely invasive



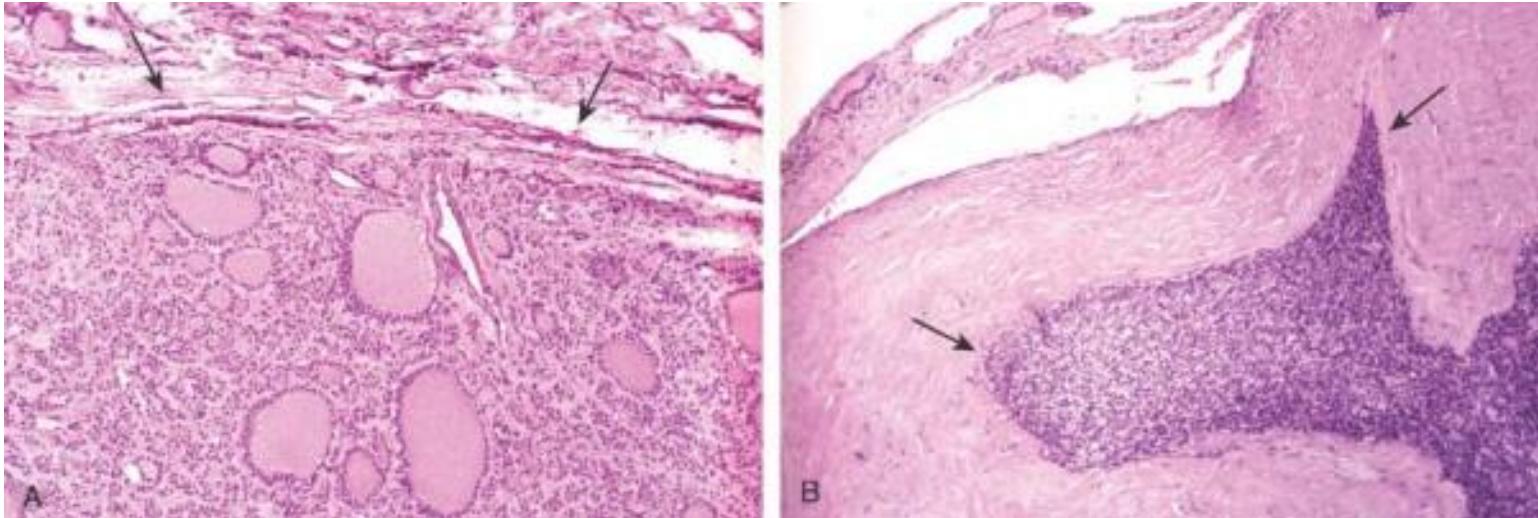
Follicular carcinoma

- Composed of closely packed follicular structures



- Distant blood borne metastasis occurs to bone and lung
- Prognosis is worse than that of papillary carcinoma

Follicular lesions

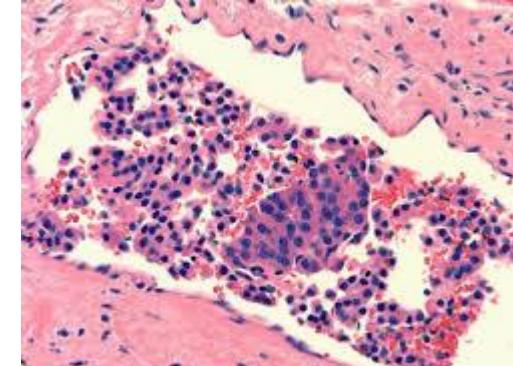


Follicular Adenoma

- Thin capsule
- No capsular invasion
- Compressed normal thyroid
- usually present external to capsule

Follicular Carcinoma

- Thick capsule
- Capsular invasion present
- May have vascular invasion



Papillary thyroid carcinoma

- Accounts for about 60-70% of all thyroid cancers.
- Has the best prognosis of all thyroid cancers
- Occurs in young
- 3 times more commoner in females than men.
- Lymphatic infiltration and metastasis is the way of spread.
- Can present with cervical lymphadenopathy without thyroid enlargement

Papillary thyroid carcinoma morphology

- Small to larger size
- Single lesion or multifocal
- Solid or cystic
- Papillary excrescences may be seen
- Could be
 - well encapsulated –good prognosis
 - widely infiltrative –bad prognosis

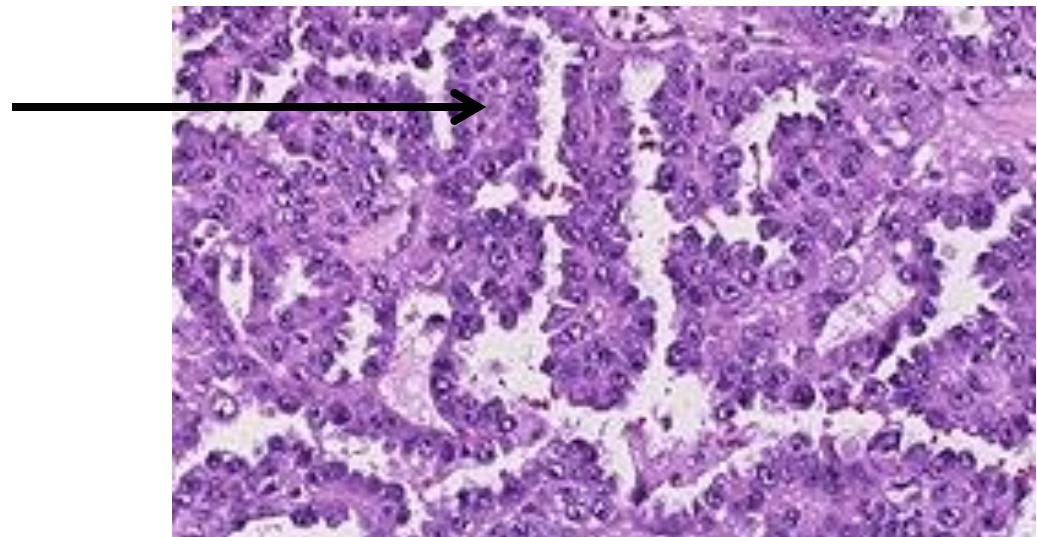


Papillary thyroid carcinoma--microscopy

- Fronds of tissue with papillary pattern
- Papillae have a thin fibro-vascular cores
- Papillae are lined by optically clear nuclei (Orphan Annie Nuclei)
- Cells show
 - Nuclear grooving
 - Nuclear overlapping
 - Intranuclear inclusions
- Psammomatous calcifications are seen in about 50 % of cases.

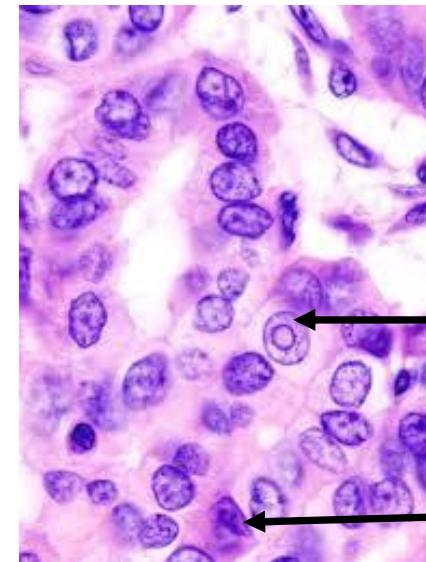
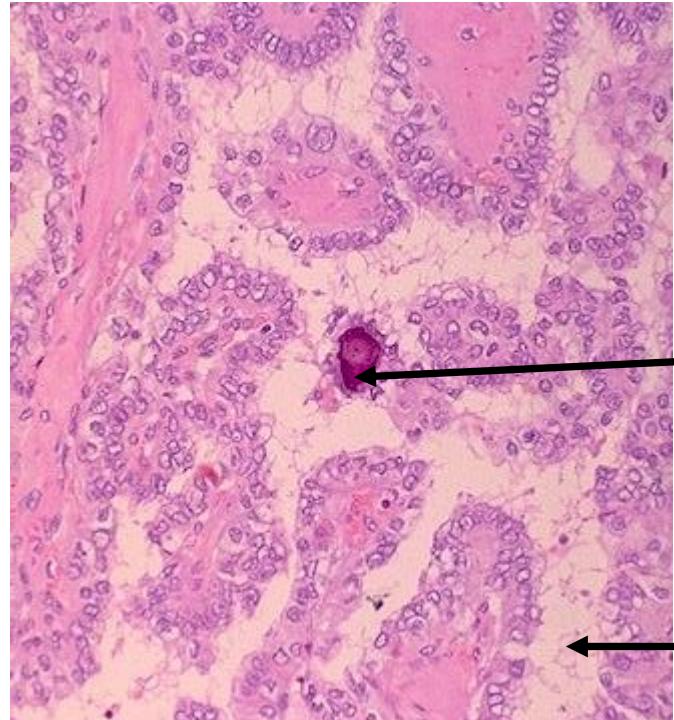
Papillary thyroid carcinoma--morphology

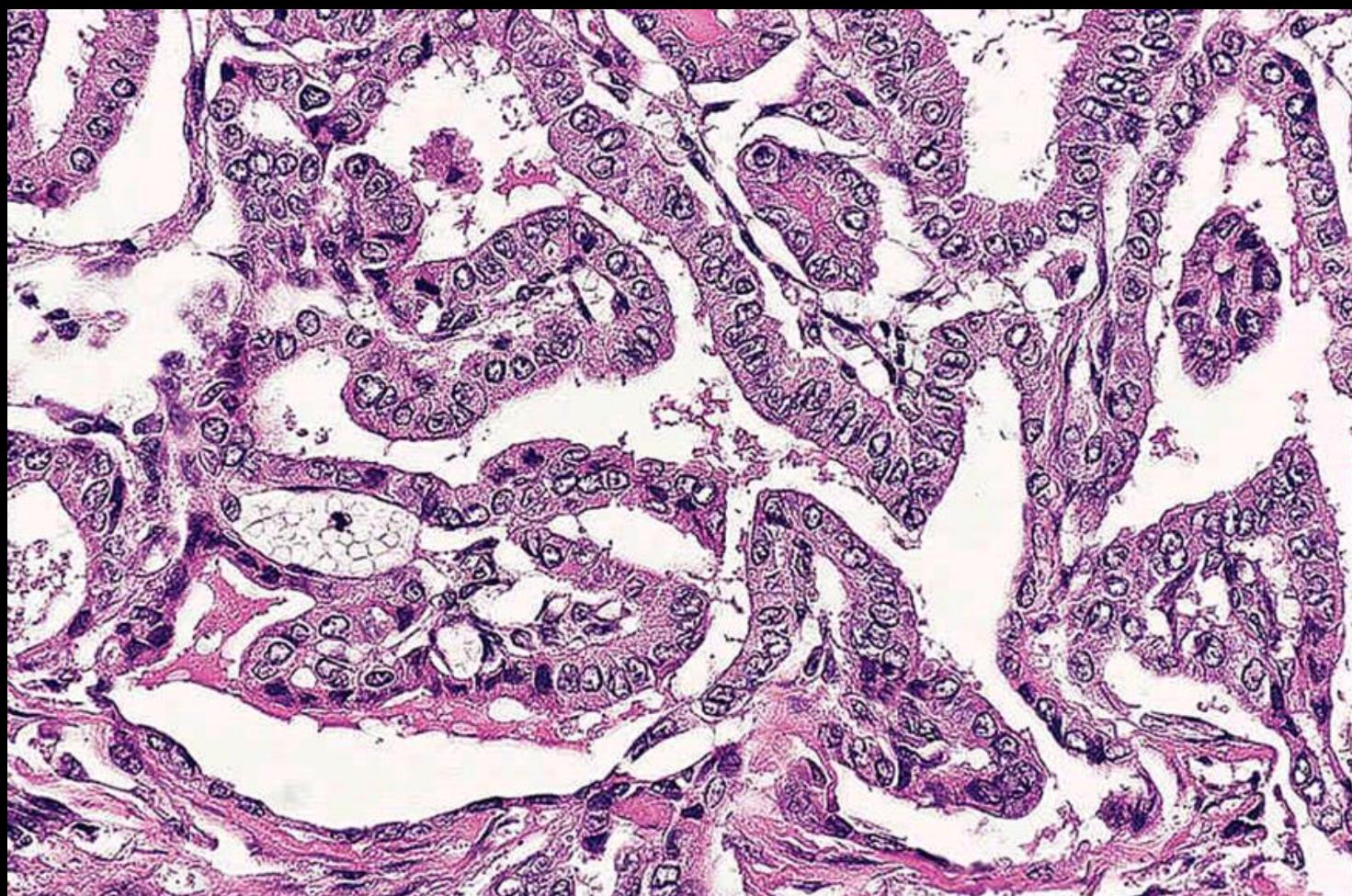
Papillae with fibrovascular cores



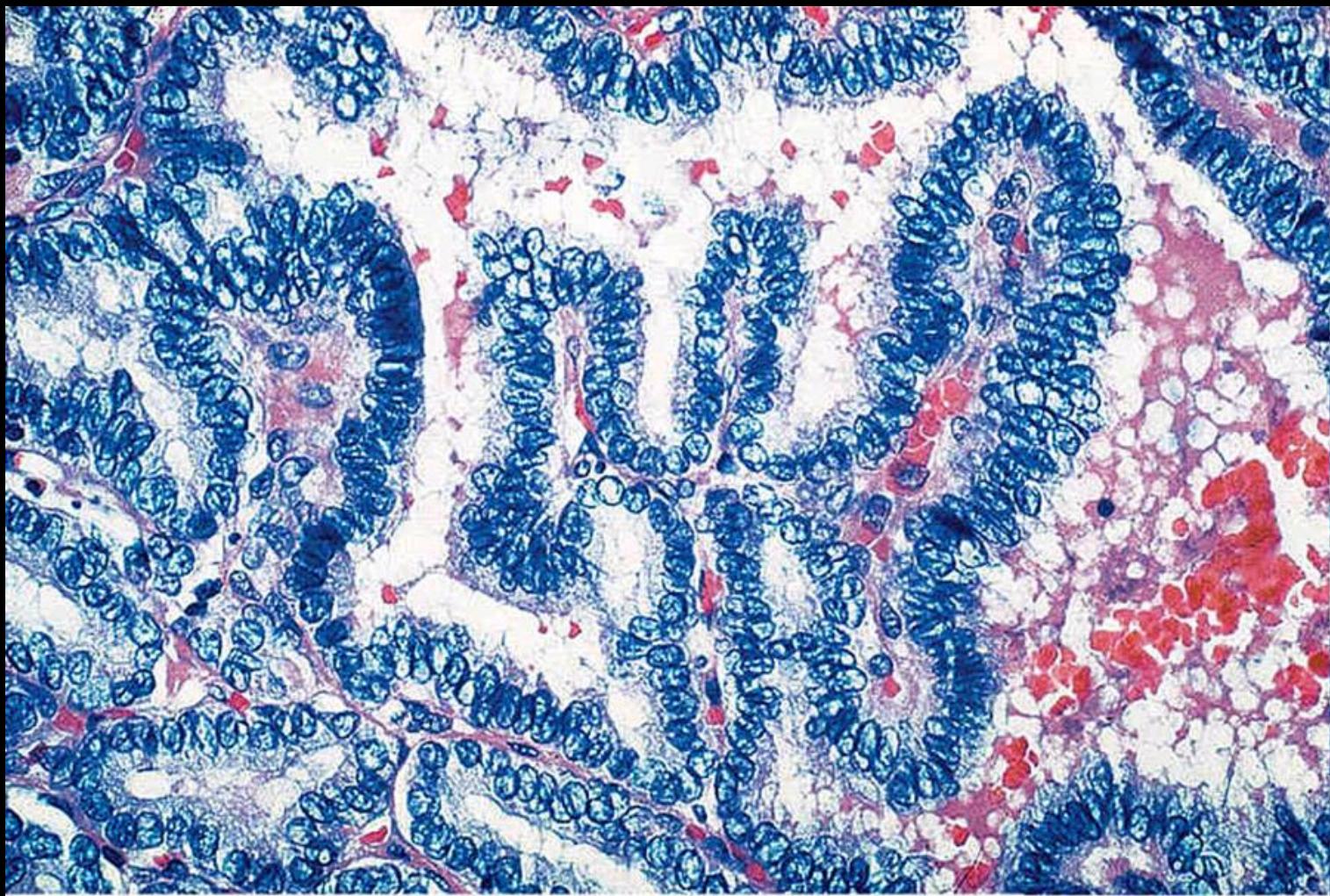
Psammomatous calcifications

Clear nuclei

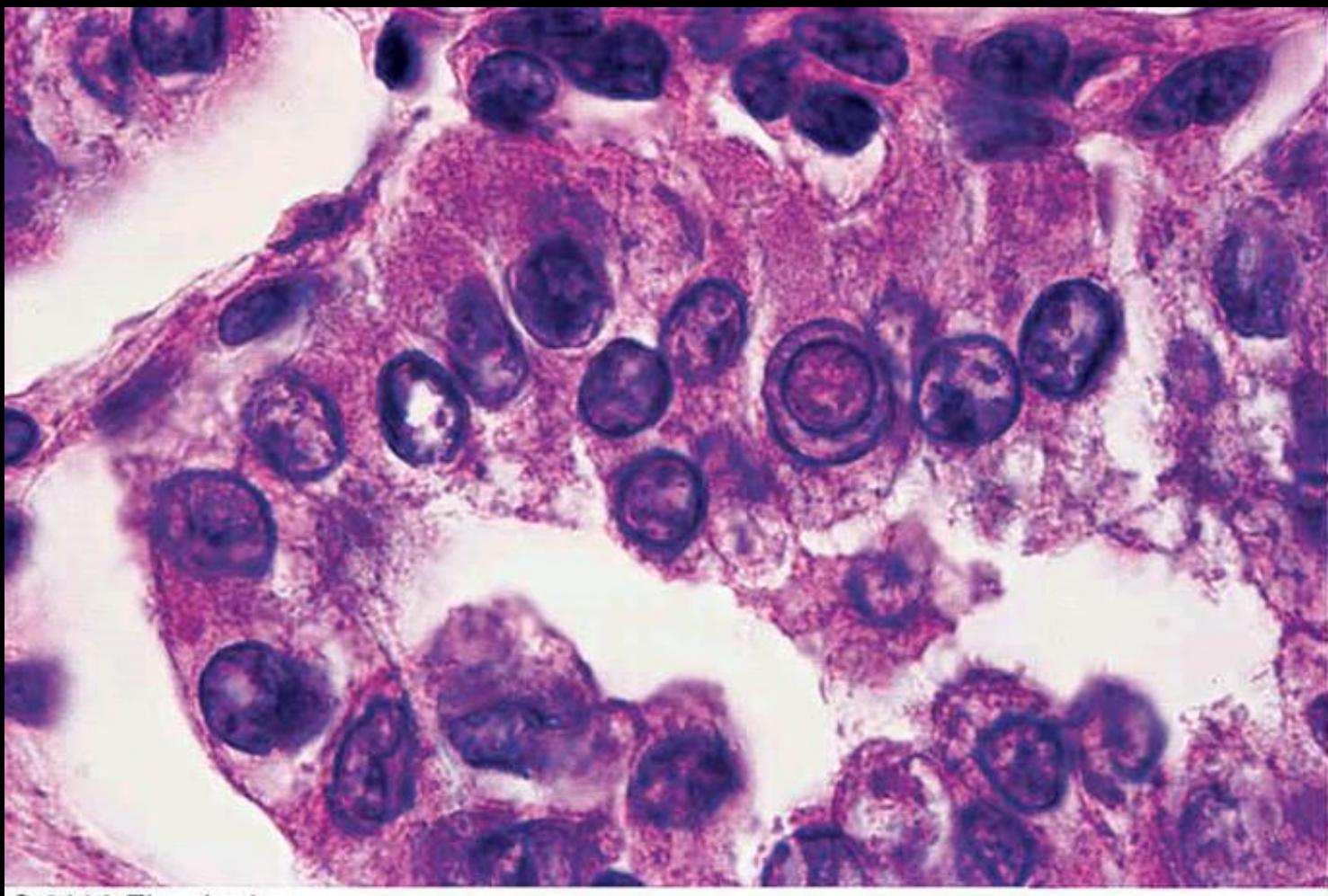




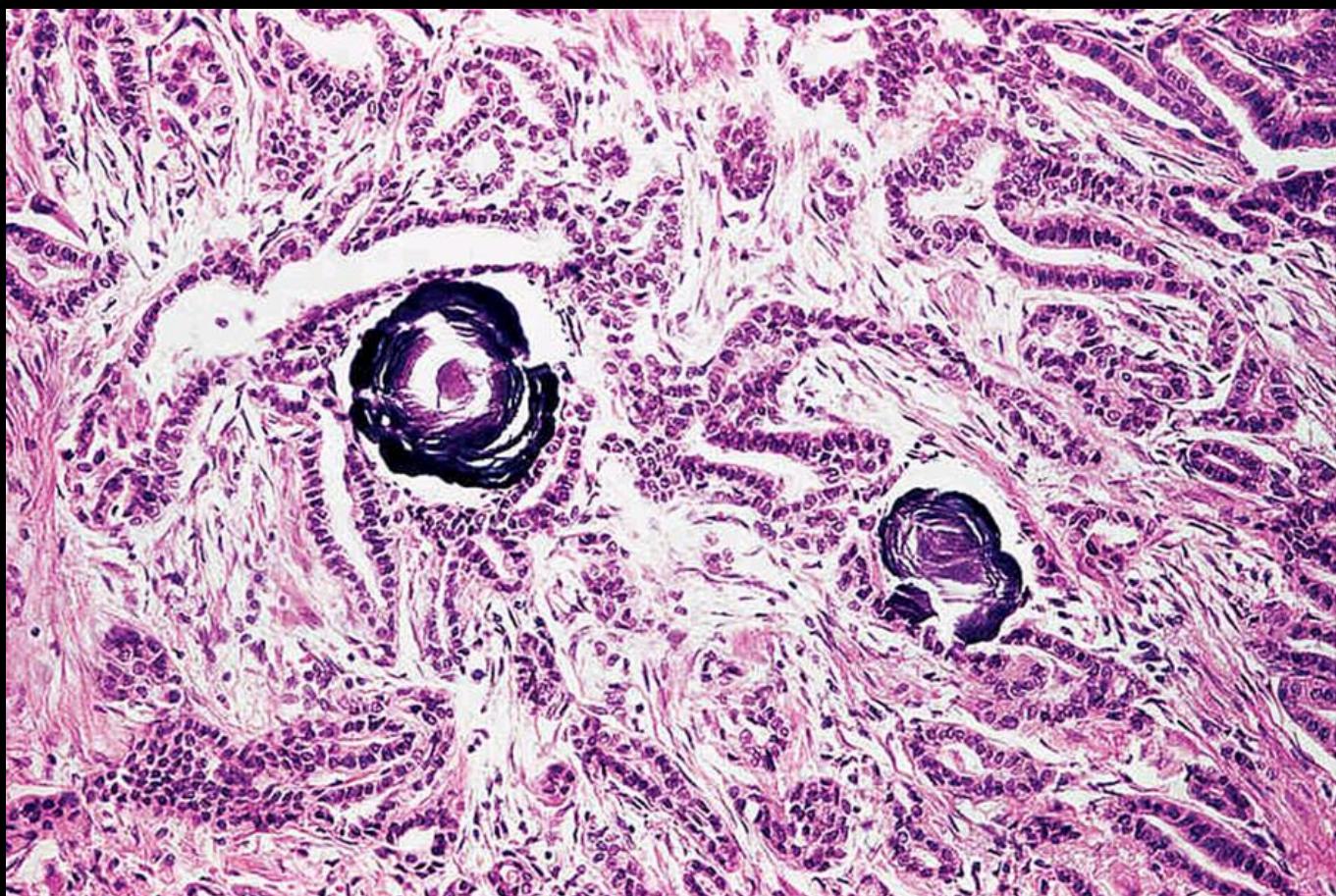
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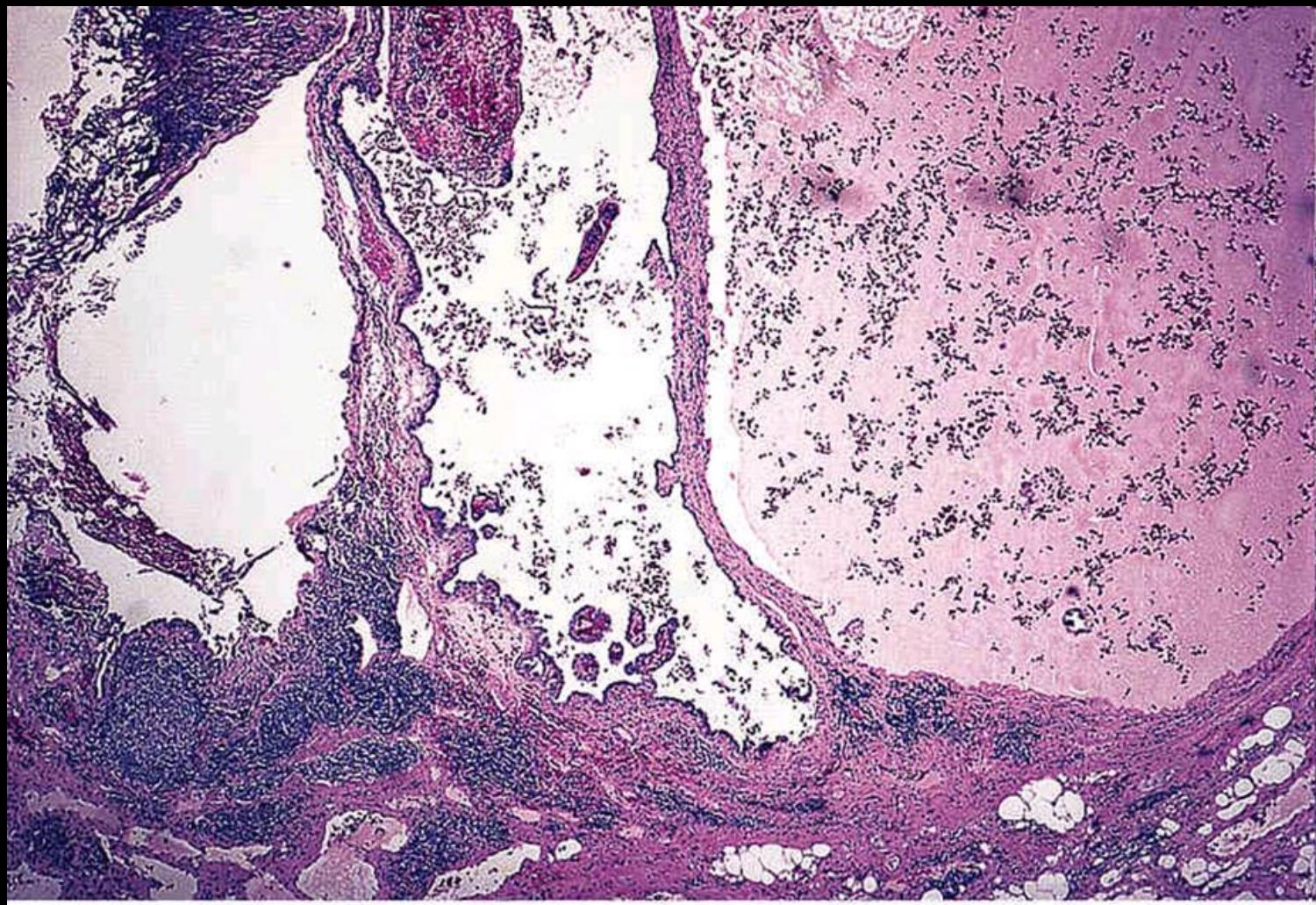
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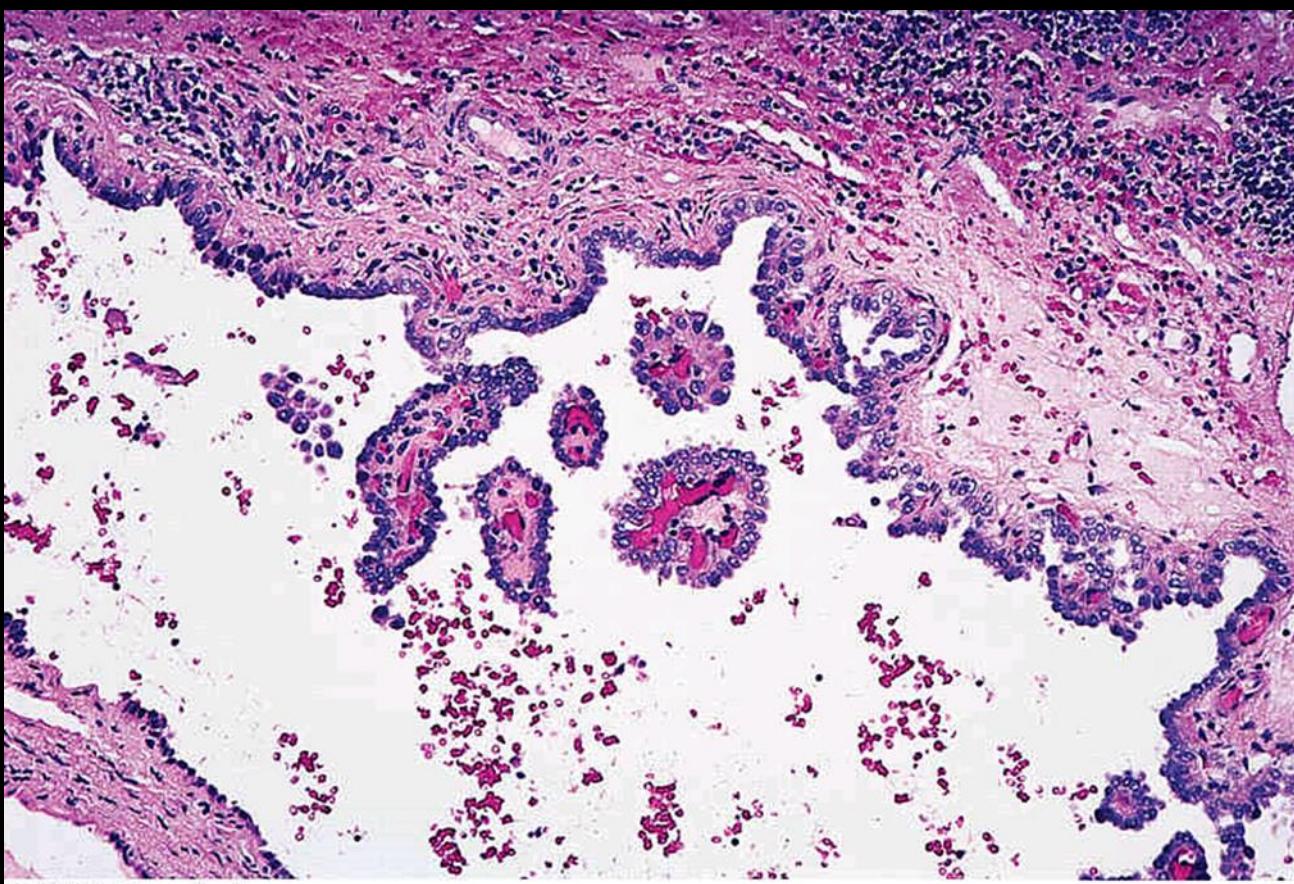
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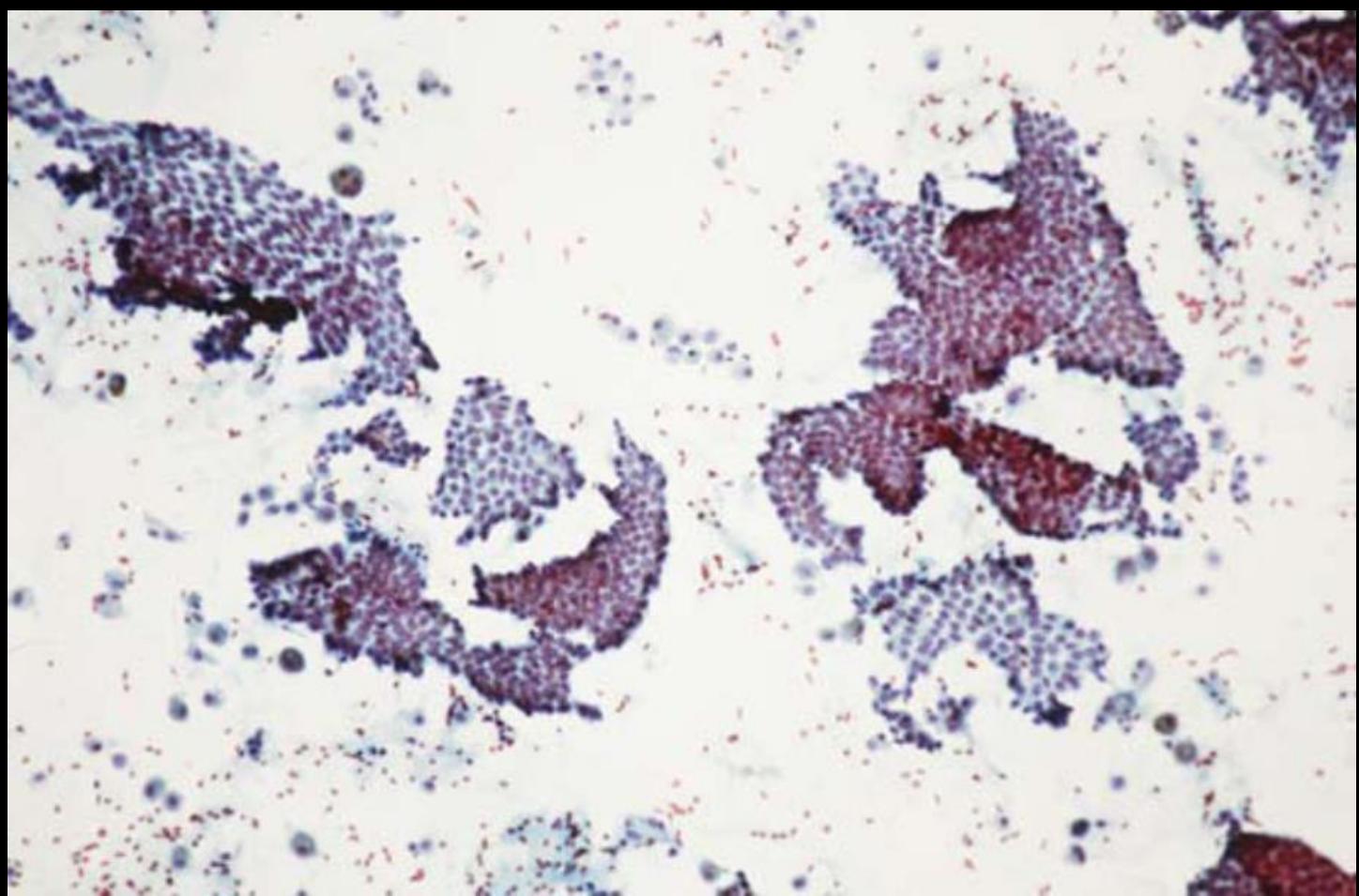
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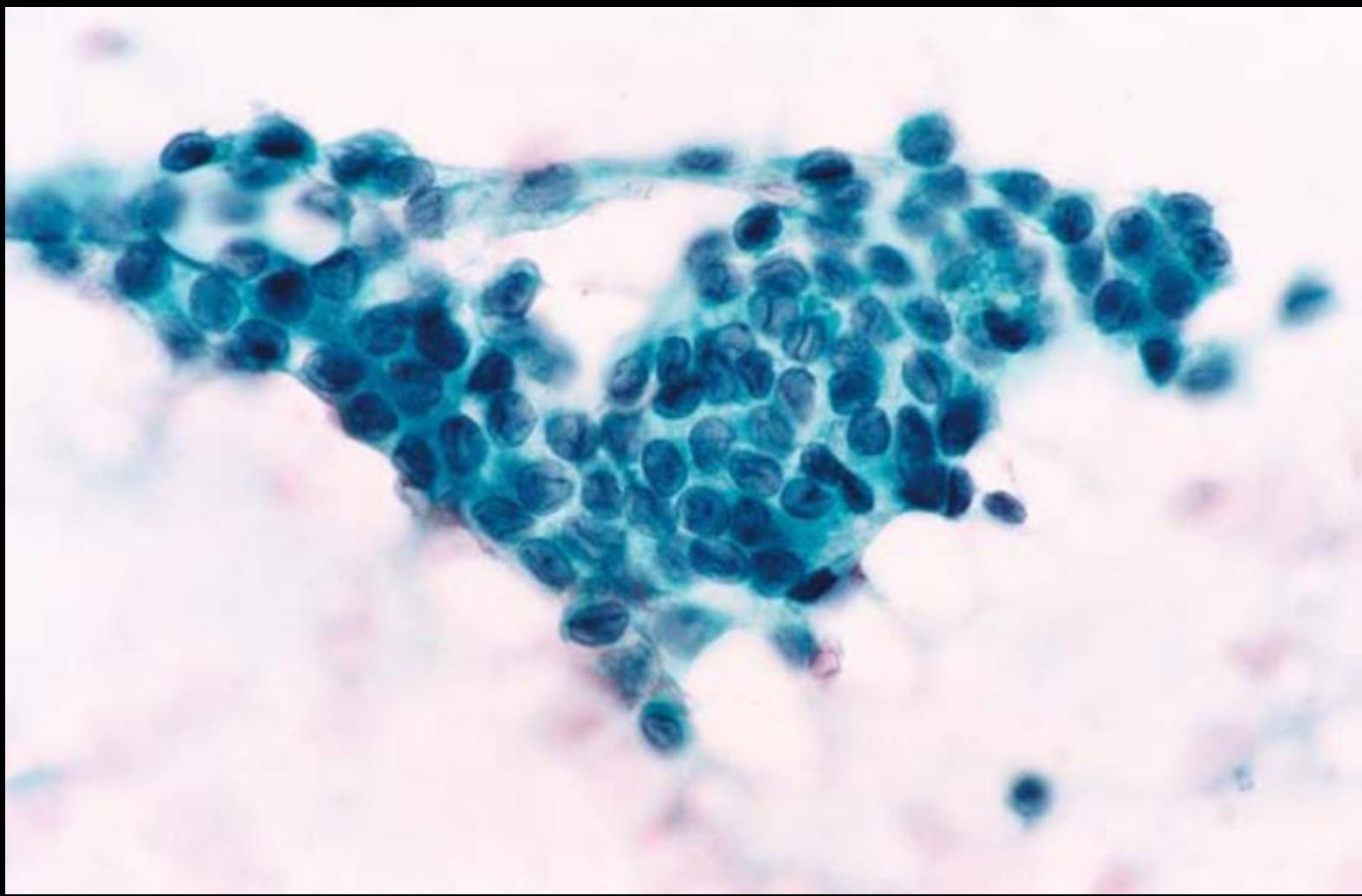


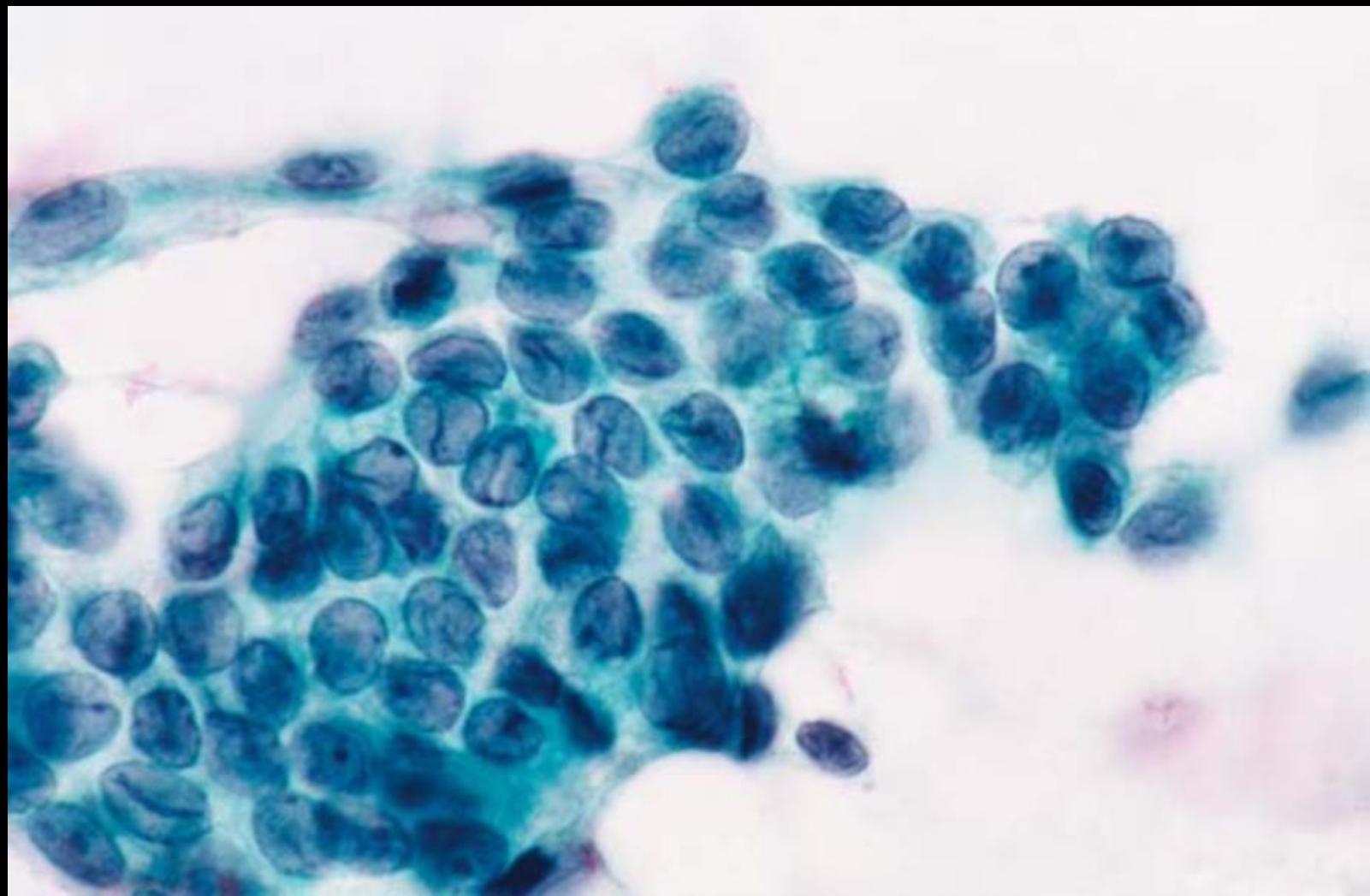
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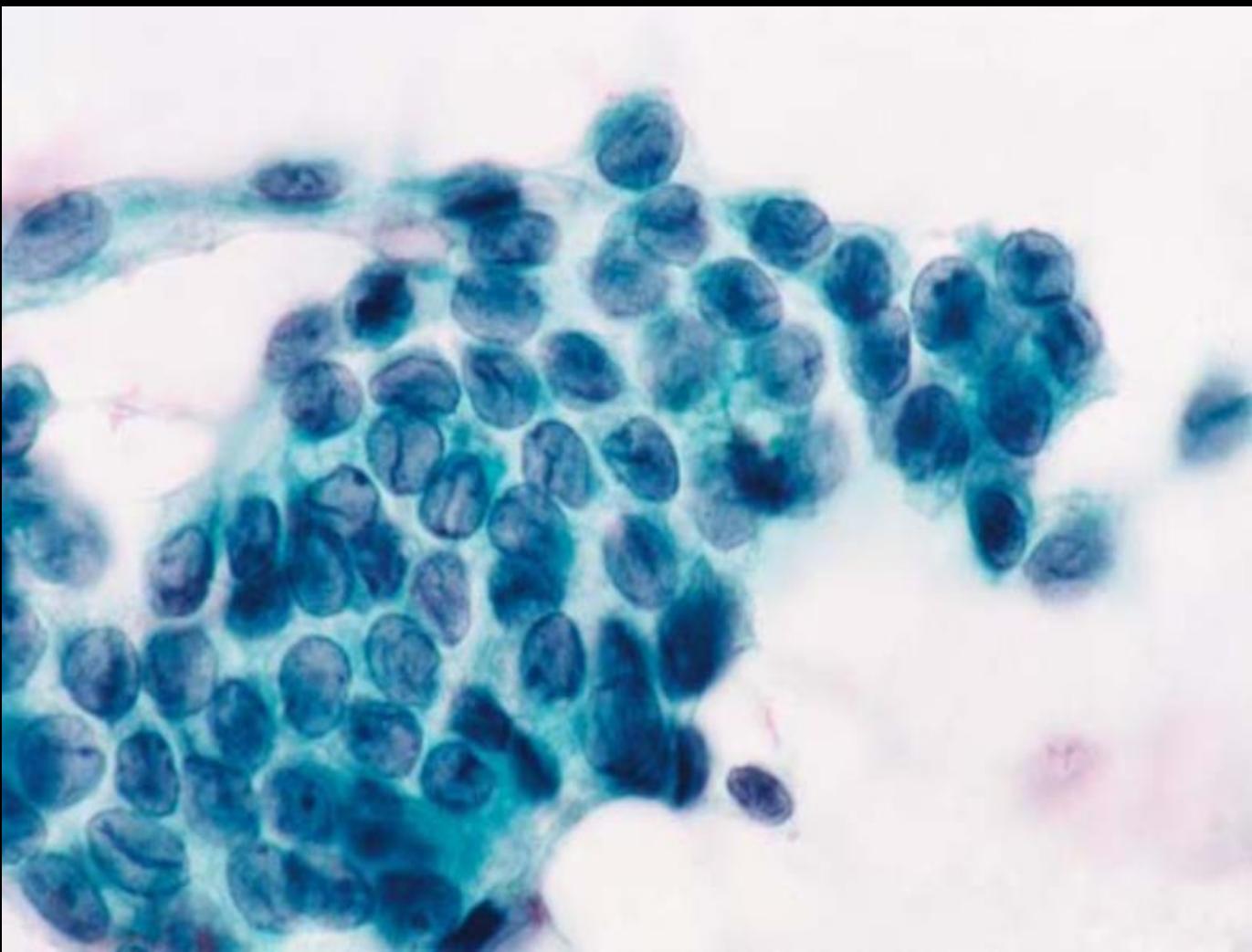


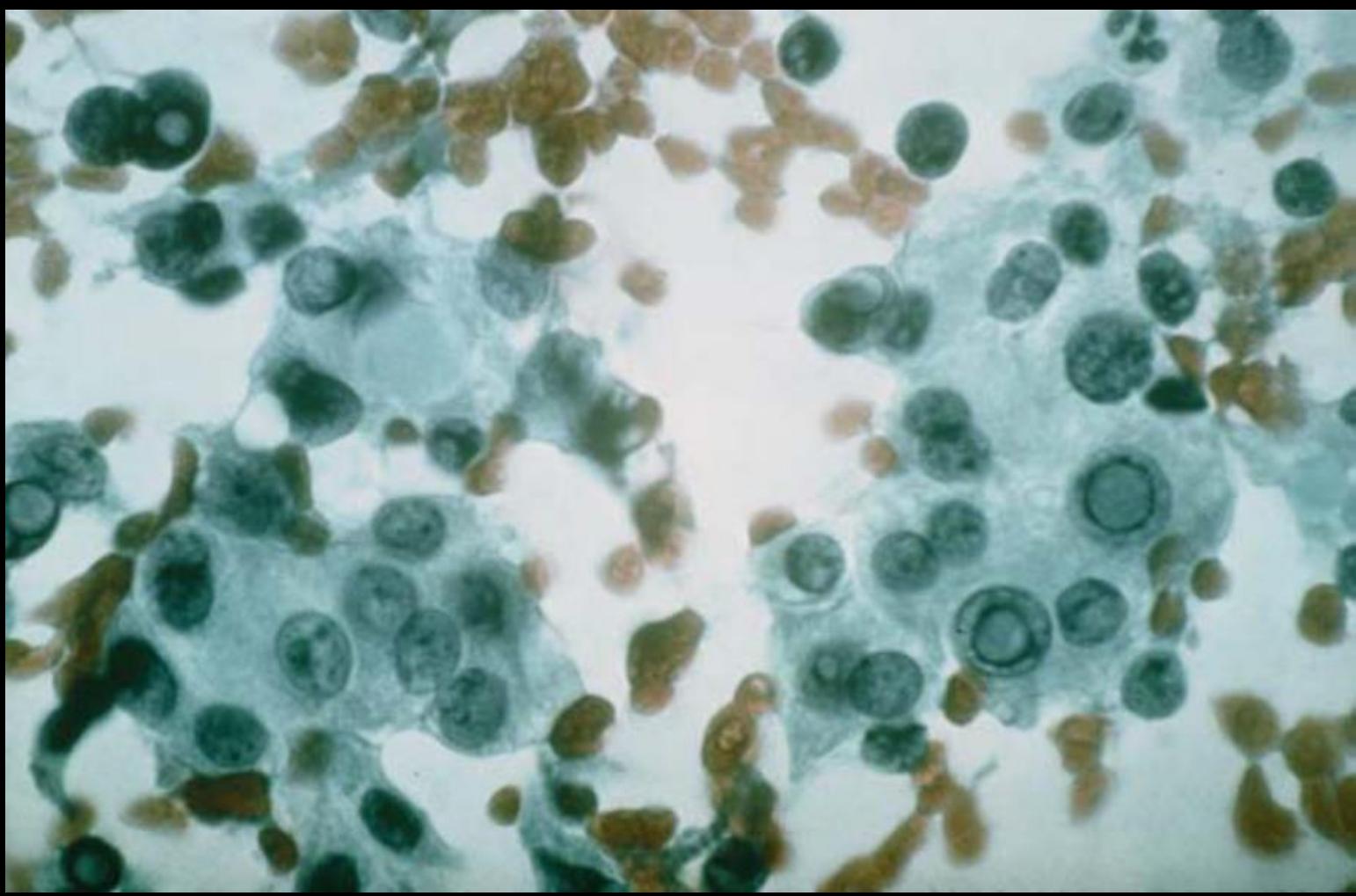
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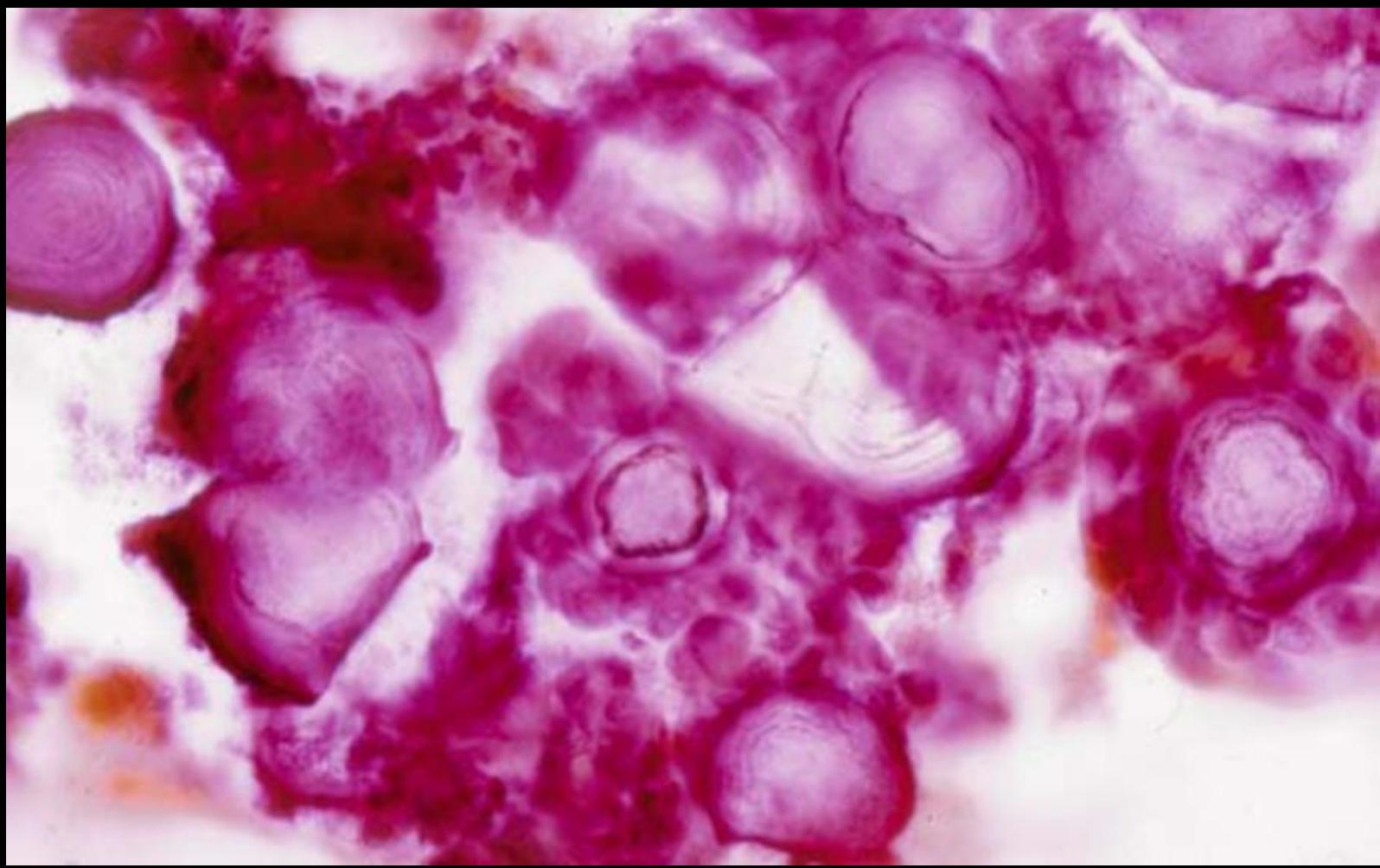








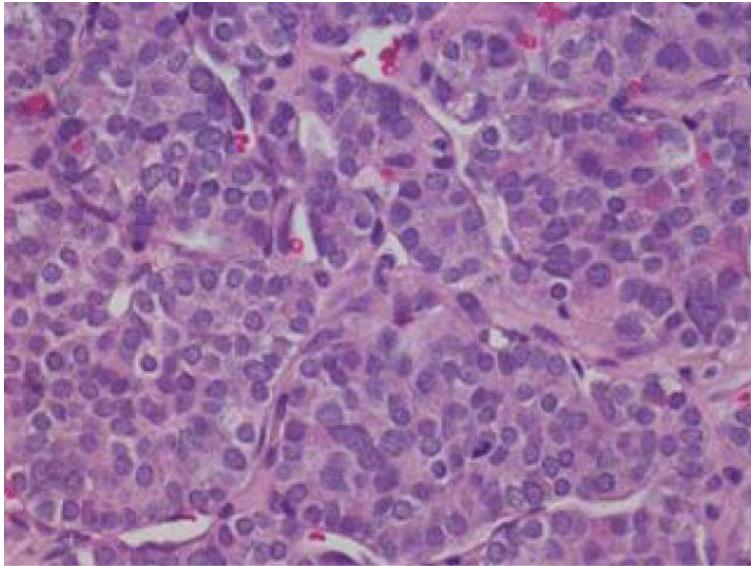




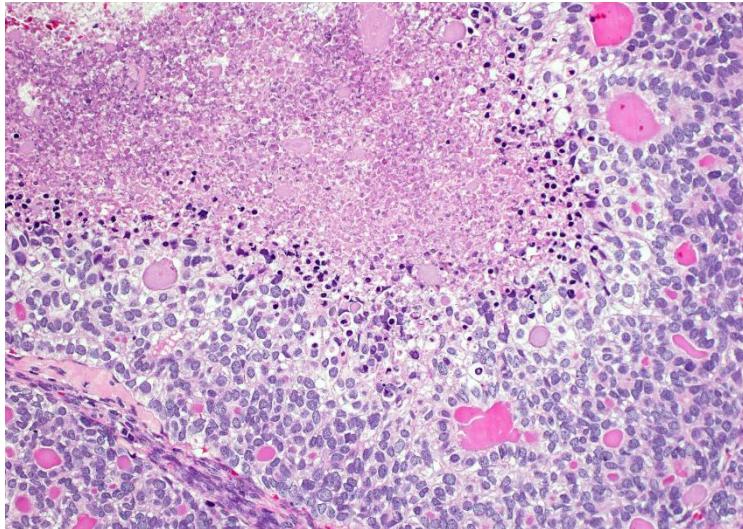
Poorly differentiated thyroid carcinoma

- Malignant follicular cell neoplasm with limited evidence of follicular cell differentiation
- Intermediate clinical behavior between well differentiated (FTC & PTC) and anaplastic carcinoma
- Diagnostic criteria(Turin consensus)
- Solid / trabecular / insular growth pattern
- No nuclear features of papillary carcinoma
- Presence of at least one of following: convoluted nuclei, ≥ 3 mitotic figures/10 HPF, tumor necrosis

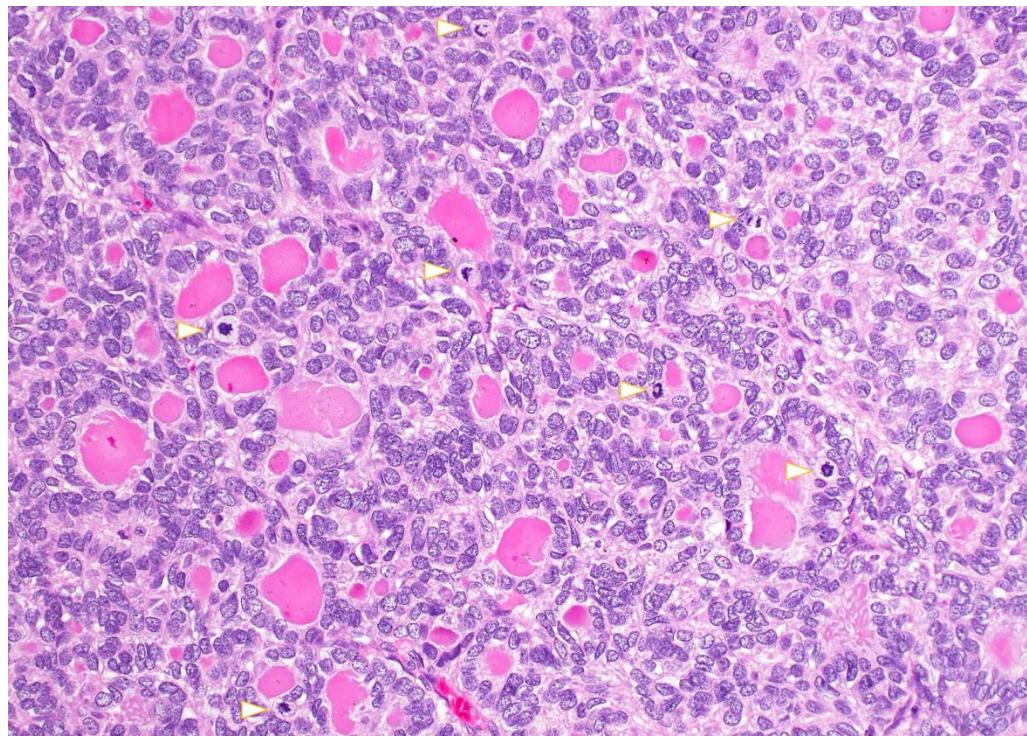
Poorly differentiated thyroid carcinoma



Solid / trabecular / insular growth pattern



Tumor necrosis



Brisk mitoses

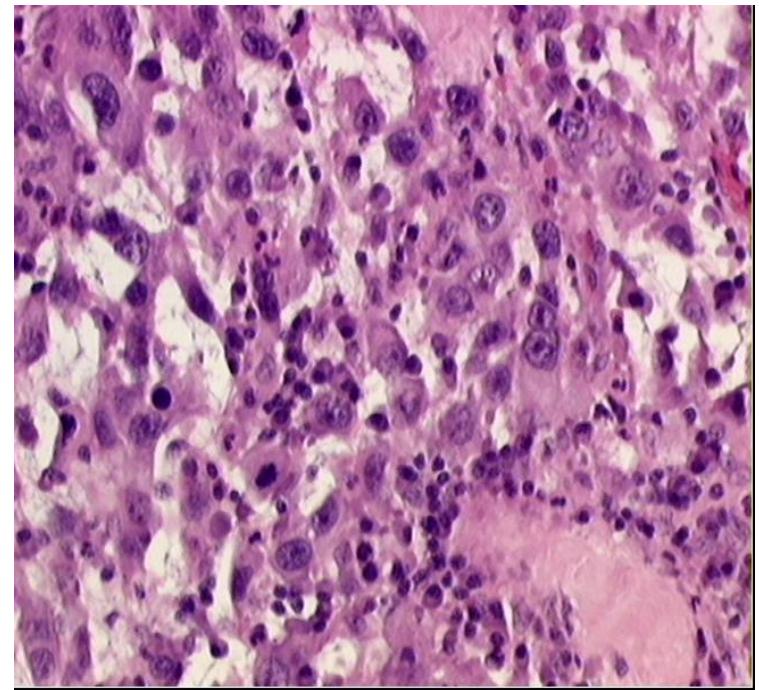
Anaplastic carcinoma

- Undifferentiated tumors of the thyroid follicular epithelium
- Aggressive tumors
- Mortality rate approaching 100%
- Fewer than 5% of all thyroid cancers
- Mean Age = 65 yrs
- 50% of the patients have a history of multinodular goiter

Anaplastic carcinoma

Composed of highly anaplastic cell

- Large , **pleomorphic** cells, including occasional osteoclast-like multinucleate giant cells
- **spindle** cells with a sarcomatous appearance
- **small** cells



Medullary carcinoma of thyroid

- Arise from the parafollicular C cells in the thyroid
 - **Familial medullary thyroid carcinomas**
 - Occur in multiple endocrine neoplasia type 2 (MEN-2) and are associated with germ-line *RET* protooncogene mutations
 - Bilateral
 - Occurs in young
 - **Sporadic medullary thyroid carcinomas**
 - Unilateral
 - Middle age
- Therefore if a medullary CA is identified it is important to screen the family members with serum calcitonin assay

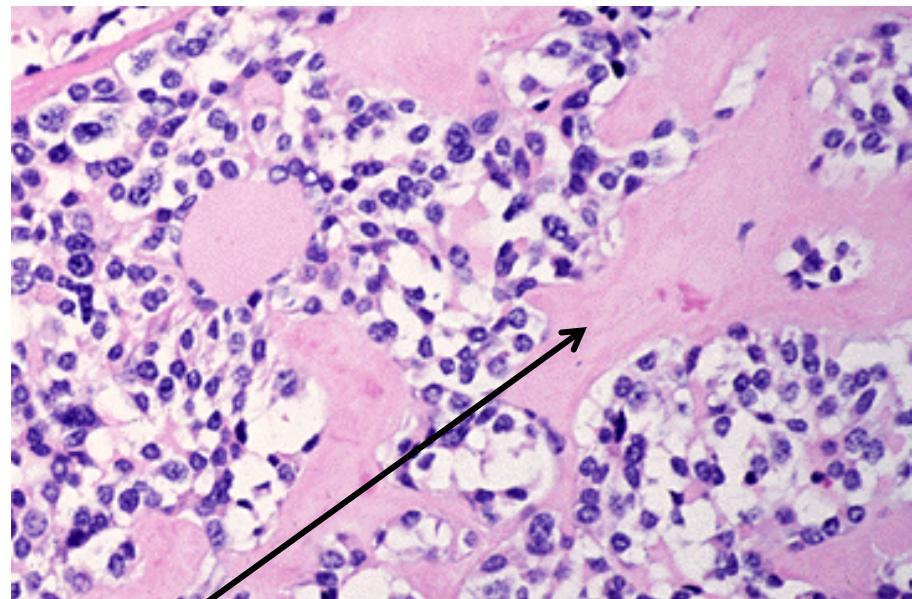
Medullary carcinoma of thyroid

- Solid pattern of growth
- Do not have connective tissue capsules



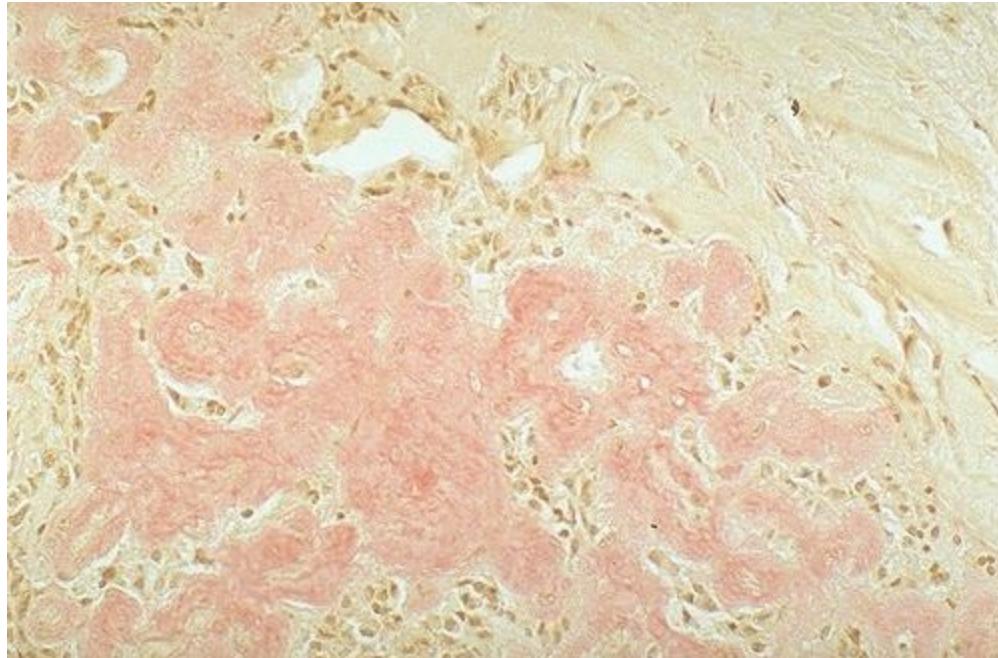
Medullary carcinoma of thyroid

- Composed of polygonal to spindle-shaped cells
 - may form nests, trabeculae, and even follicles



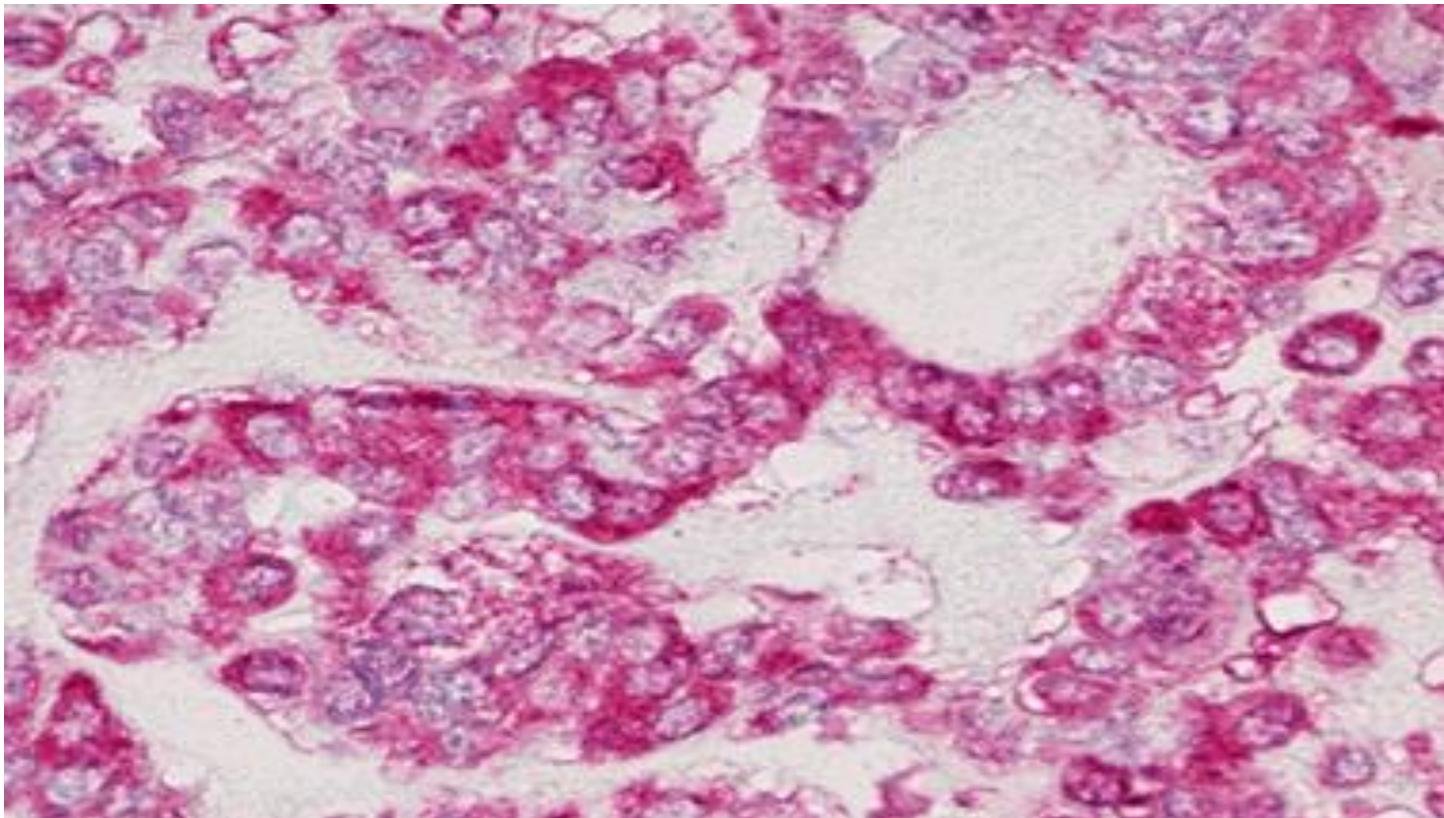
- Acellular **amyloid deposits**, derived from altered calcitonin molecules, are present in the adjacent stroma in many cases

Medullary carcinoma of thyroid



Amyloid stains red with Congo red
stain

Medullary carcinoma of thyroid



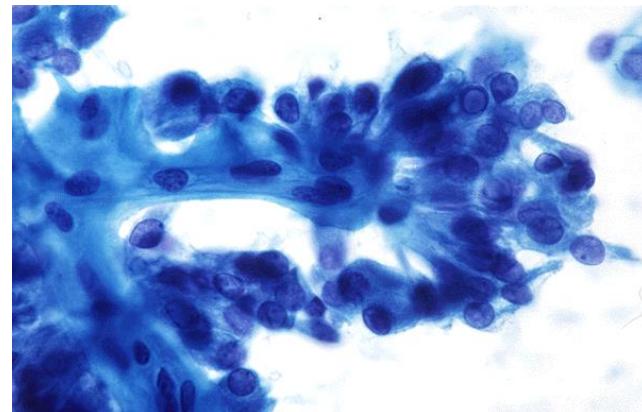
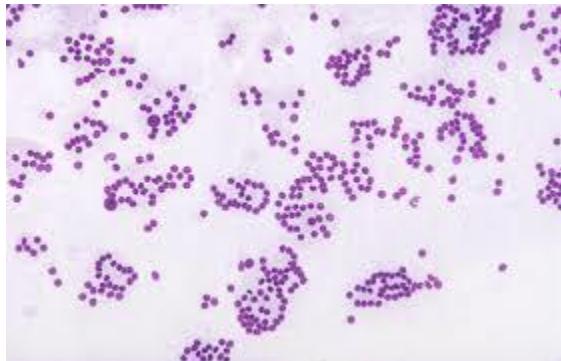
- Immunohistochemical anti-calcitonin antibody stain showing strong red positivity

Clinical approach in thyroid problems

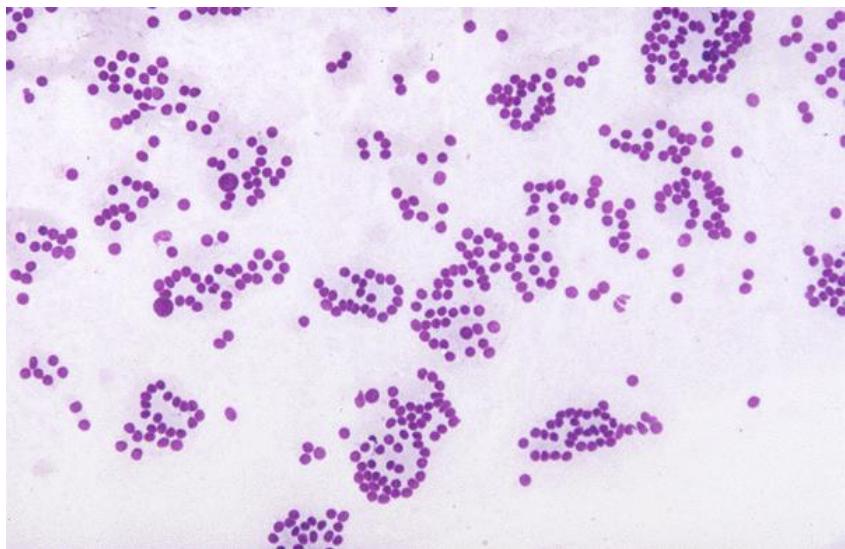
- Goitre
 - Diffuse
 - Multinodular
 - Solitary nodule
- Approach to STN
- FNAC of thyroid gland
 - technique
 - Advantages
 - Disadvantages

FNAC in thyroid lesions

- Diagnostic value of FNAC
 - In follicular lesions
 - Papillary lesions
 - Thyroiditis



Follicular lesions in cytology



Could be

- Follicular adenoma
- Follicular carcinoma
- Hyperplastic nodule in a multinodular goitre

Histology is essential for further identification