Endocrine system
Thyroid gland part 2

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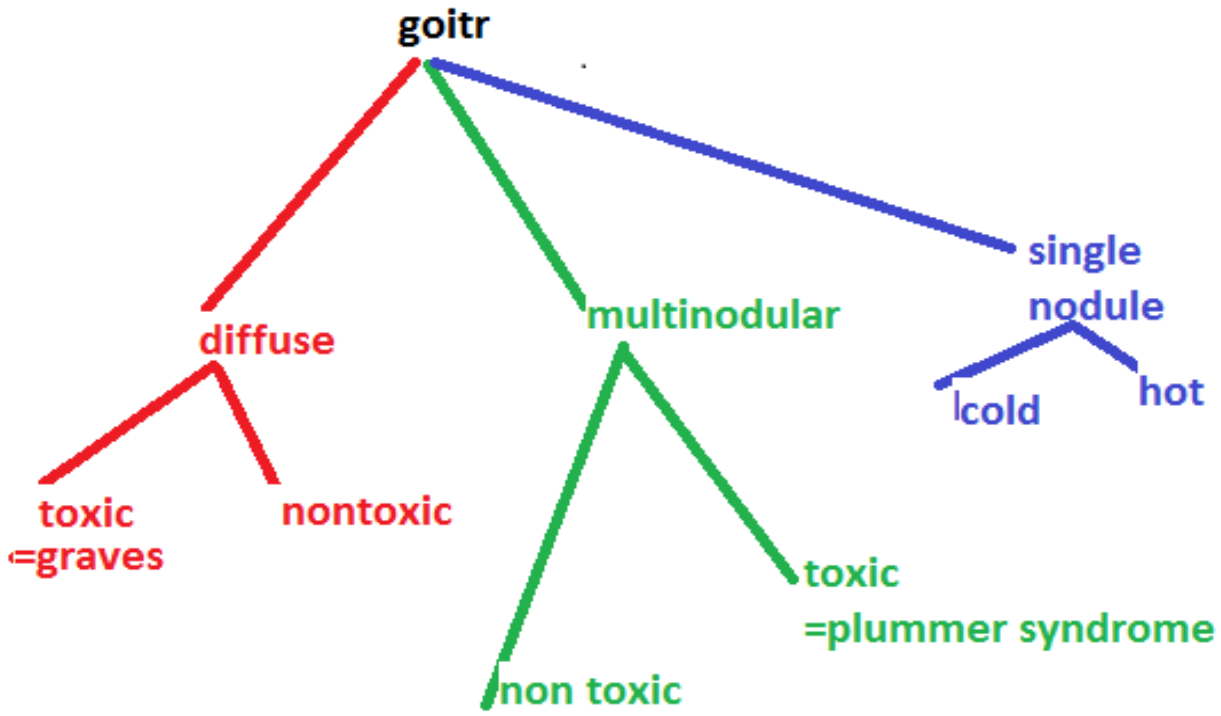
MD, FRCPath

Goiter


goitr
diffuse
multinodular
single
nodule
toxic
=graves
nontoxic
cold
hot
toxic
=plummer syndrome
non toxic

DIFFUSE AND MULTINODULAR GOITER

Enlargement of the thyroid, or *goiter,* is the most common manifestation of thyroid disease

Mechanism :

- *The goiters reflect impaired synthesis of thyroid hormone* often caused by dietary iodine deficiency and this leads to to a compensatory rise in the serum TSH, which in turn causes hyperplasia of the follicular cells and, ultimately, gross enlargement of the thyroid gland .

Goiters can be endemic or sporadic.

Endemic goiter :Occurs in geographic areas where the soil, water, and food supply contain little iodine.

- The term *endemic* is used when goiters are present in more than 10% of the population in a given region.
- Such conditions are common in mountainous areas of the world, including the Himalayas and the Andes but with increasing availability of iodine supplementation, the frequency and severity of endemic goiter have declined

Sporadic goiter : Less common than endemic goiter.

- more common in females than in males, with a peak incidence in puberty or young adulthood, when there is an increased physiologic demand for T_4.
- It may be caused by several conditions, including the:

a. Ingestion of substances that interfere with thyroid hormone synthesis , such as excessive calcium and vegetables such as cabbage, cauliflower, sprouts, .

b. Hereditary enzymatic defects that interfere with thyroid hormone synthesis *(dyshormonogenetic goiter).*

-In most cases, the cause of sporadic goiter is not apparent.

MORPHOLOGY :

- Initially, the gland is diffusely and symmetrically enlarged (diffuse goiter) but later on it becomes multinodular goiter.

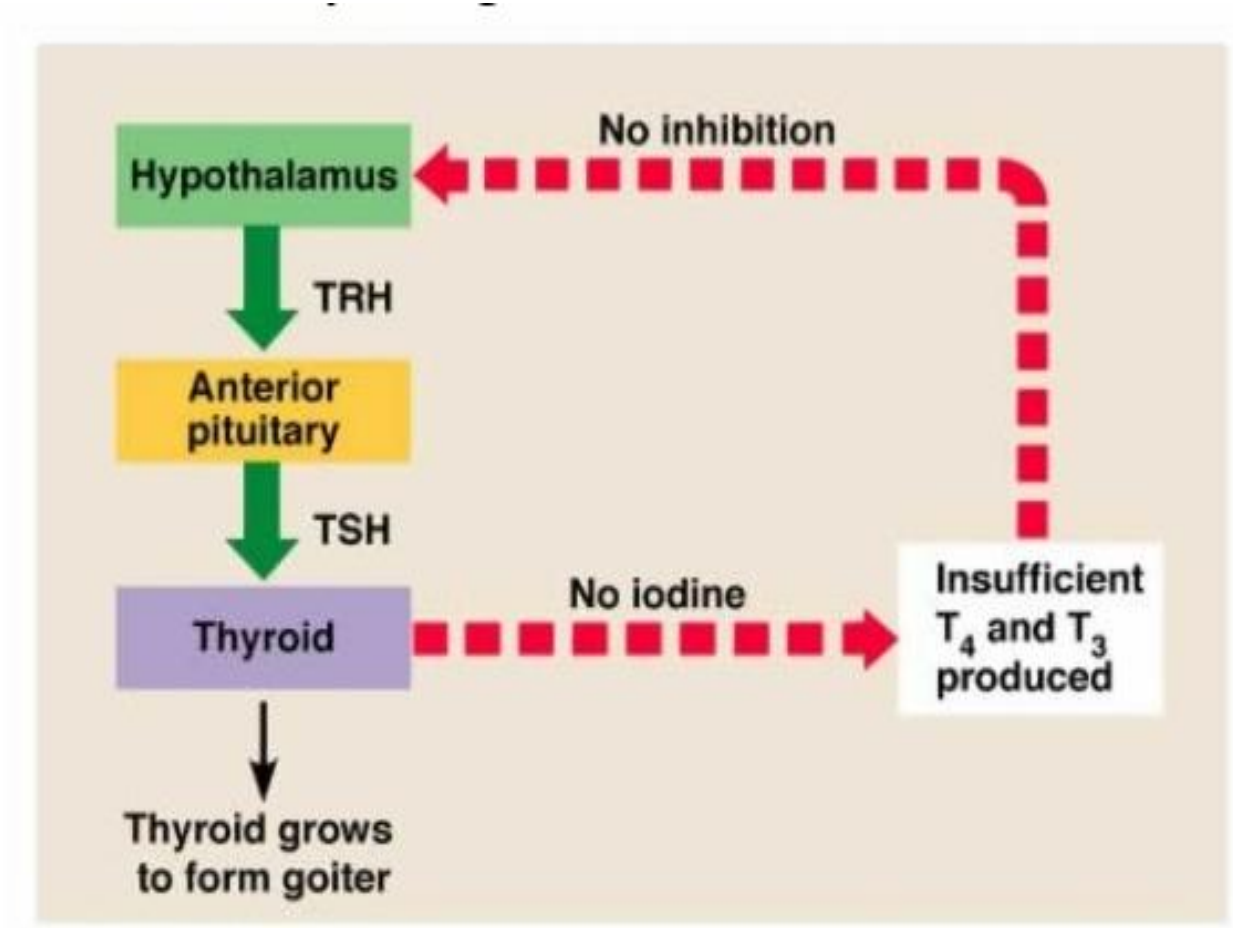
On microscopic examination,

a. The follicular epithelium may be hyperplastic in the early stages of disease or flattened and cuboidal during periods of involution.

b. Colloid is abundant in the latter periods (colloid goiter).

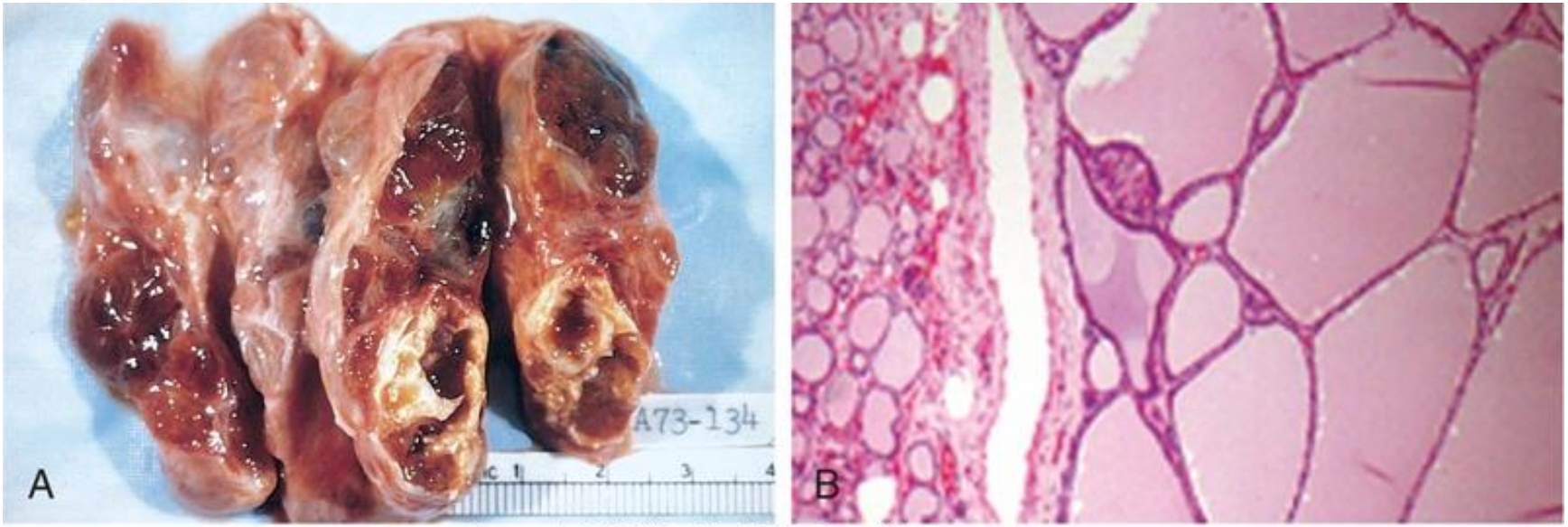
c. With time, recurrent episodes of hyperplasia and involution produce a more irregular enlargement of thee thyroid, termed multinodular goiter and virtually all long-standing diffuse goiters convert into multinodular goiters.

mechanism


Hypothalamus
No inhibition
TRH
Anterior pituitary
TSH
Thyroid
No iodine
Insufficient T_4 and T_3 produced
Thyroid grows to form goiter

Macroscopic appearance

- Multinodular goiters cause multilobulated, asymmetrically enlarged glands . Old lesions often show fibrosis, hemorrhage, calcification



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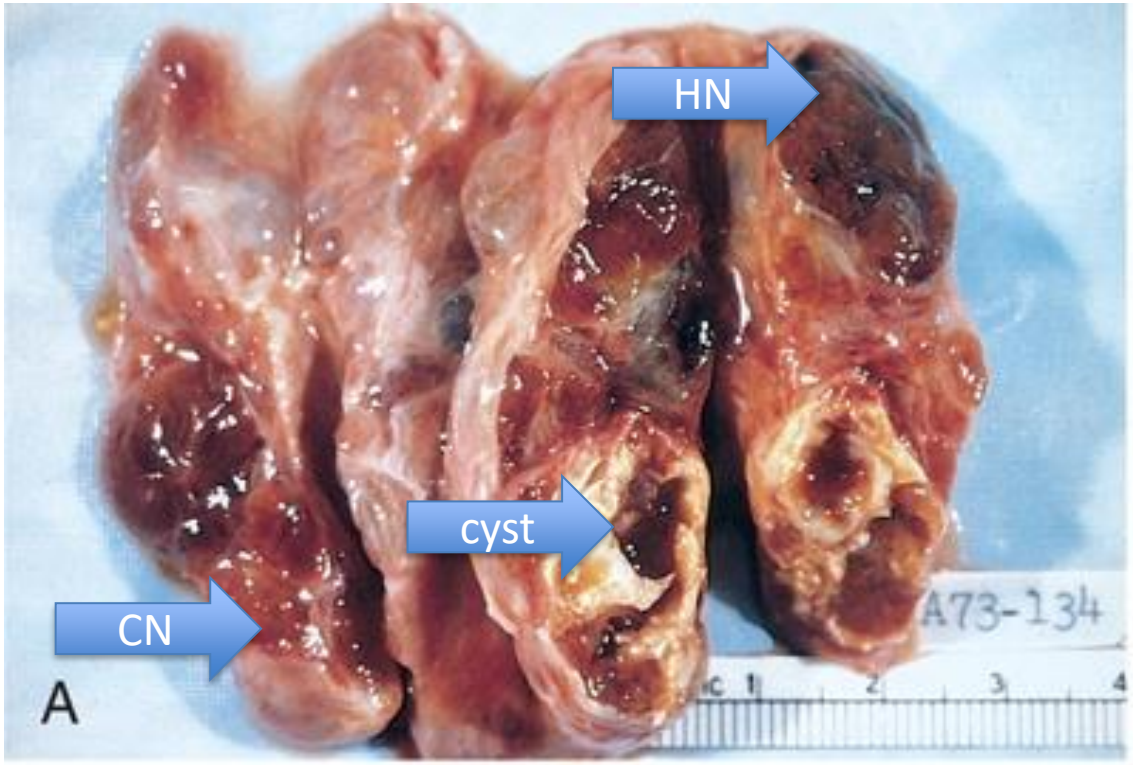
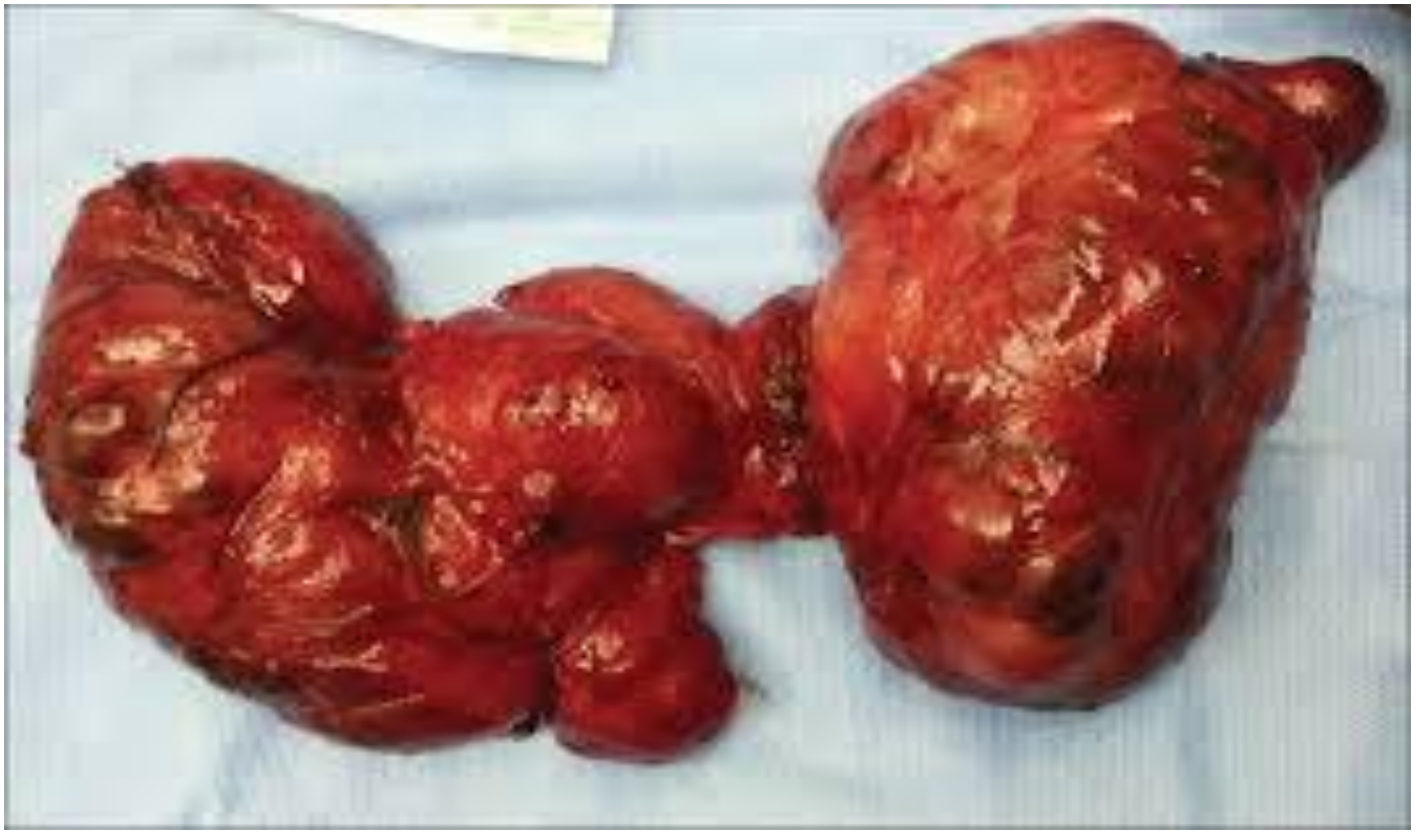
Multinodular goiter: thyroid shows several nodules, some are hemorrhagic (HN), others contain colloid (CN) and some become cystic.



multinodular goiter



Note:

- Multinodular goiters typically are hormonally silent (no hyperthyroidism)
- however, 10% of patients can manifest with thyrotoxicosis due to the development of autonomous nodules producing hormone independent of TSH stimulation and this condition, called toxic multinodular goiter or **Plummer syndrome**

Clinical Features :

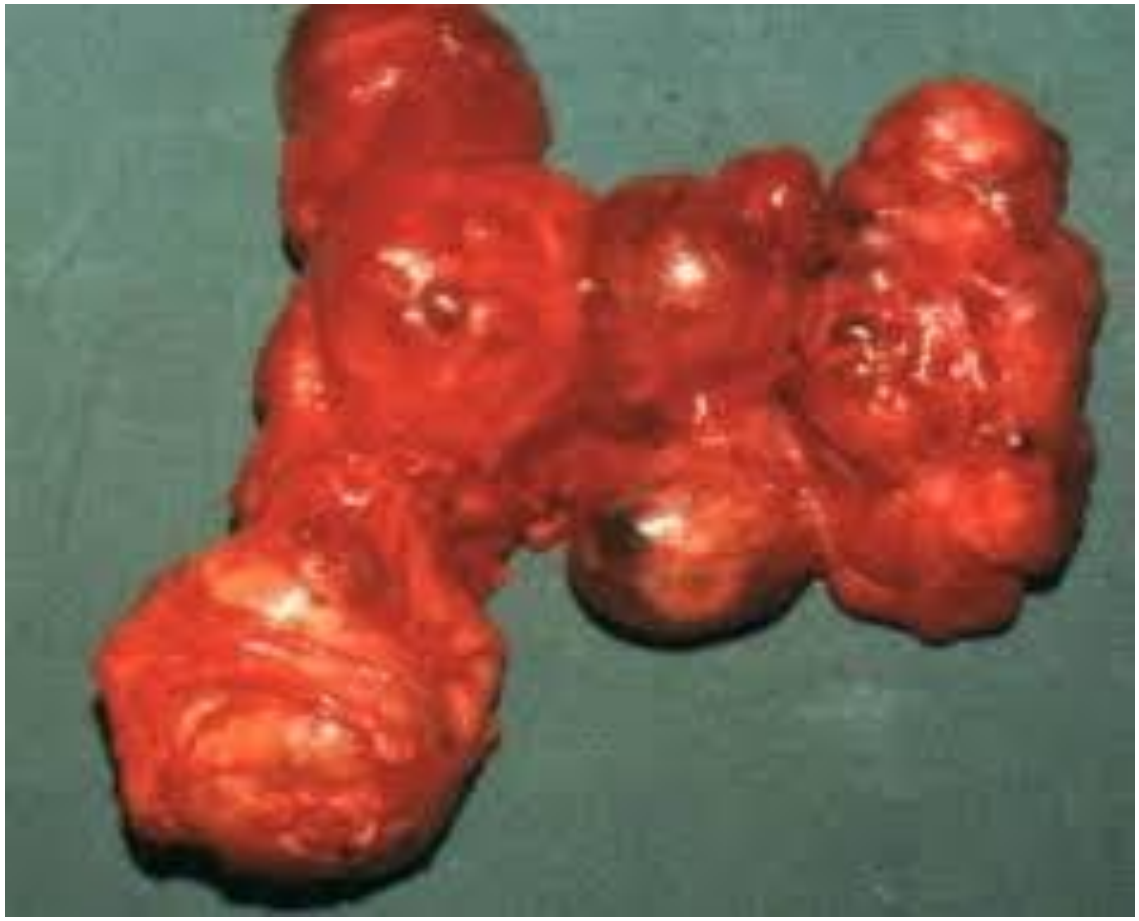
a. The dominant features are *mass effects* of the goiter

b. may cause airway obstruction, dysphagia, and compression of large vessels in the neck and upper thorax

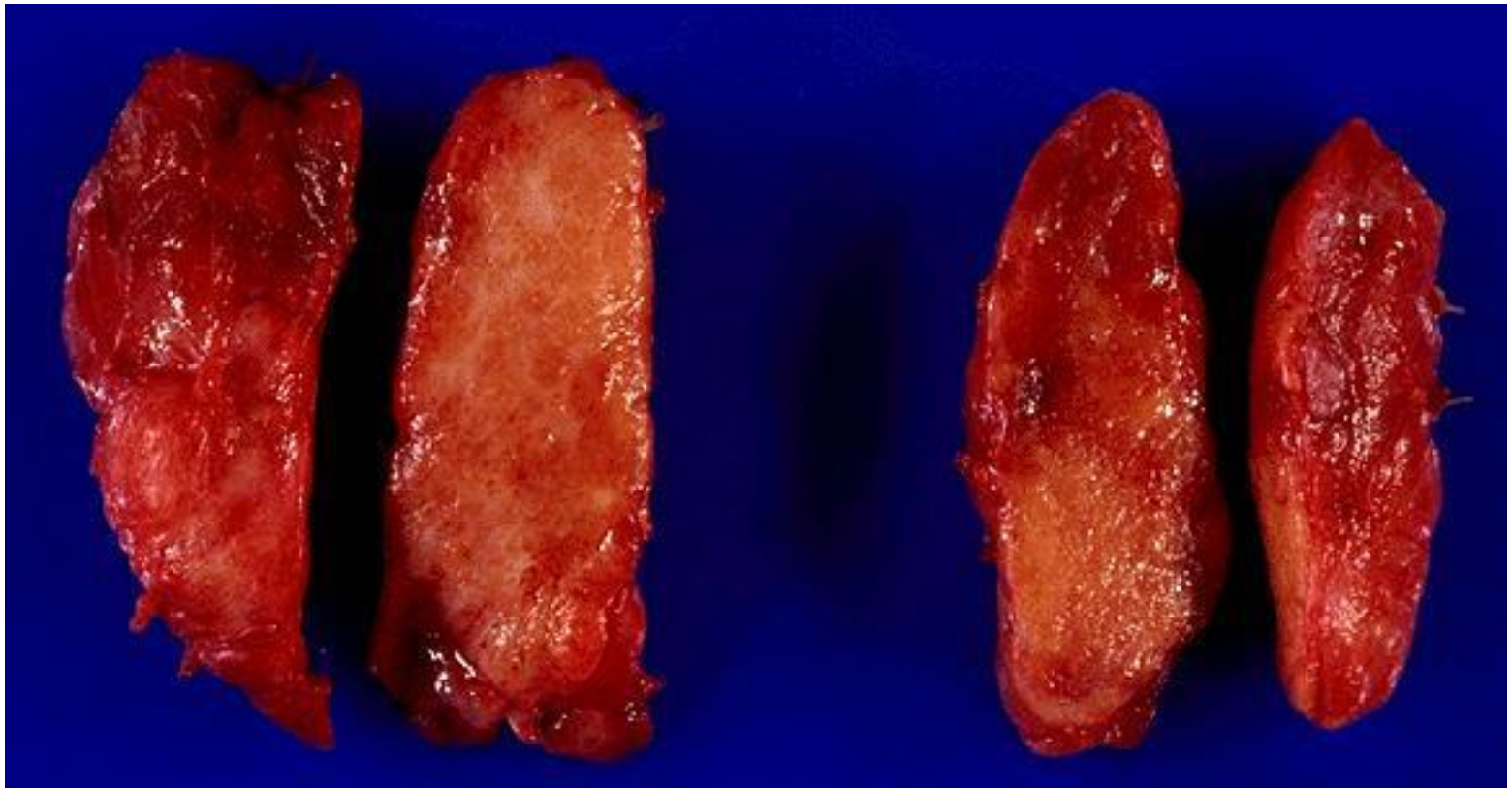
c. The incidence of malignancy in long-standing multinodular goiters is low (less than 5%) but not zero and concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms (hoarseness)

QUIZ.. What's the type of goiter on these macroscopic pictures:

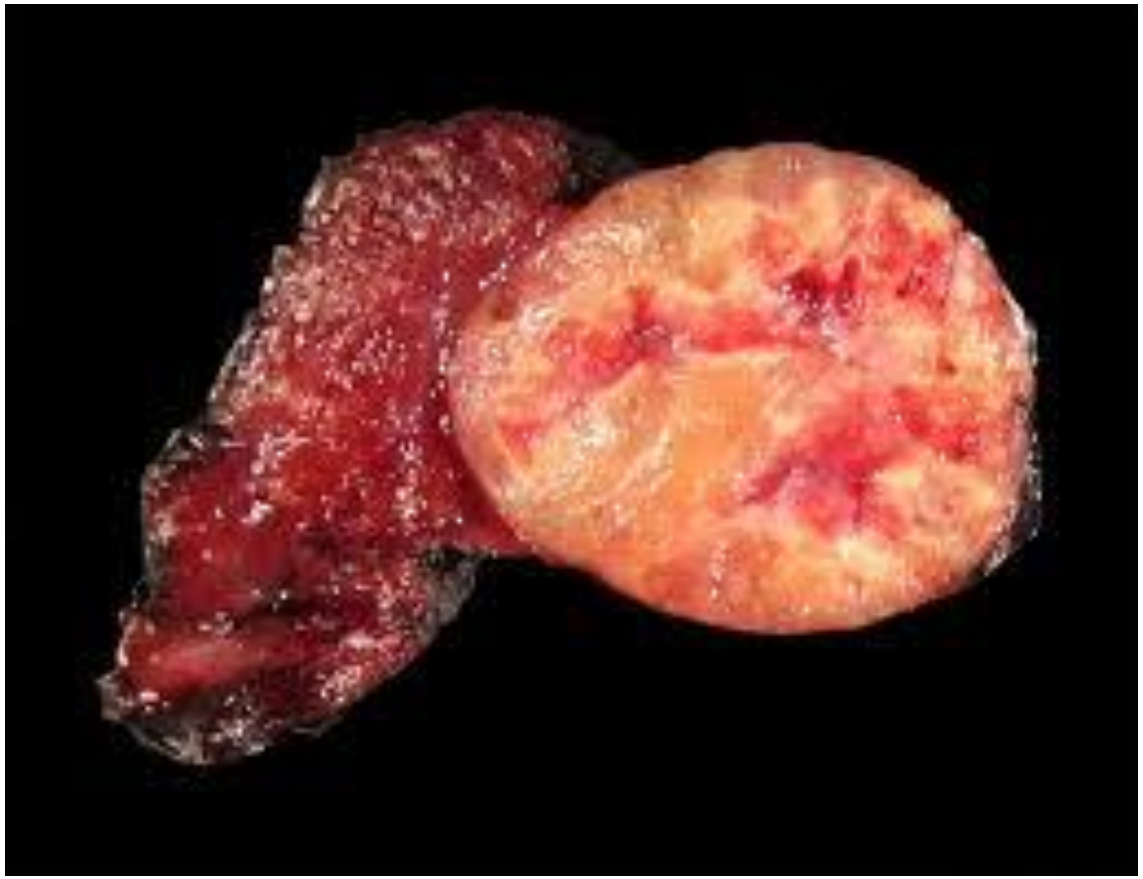
- Case A



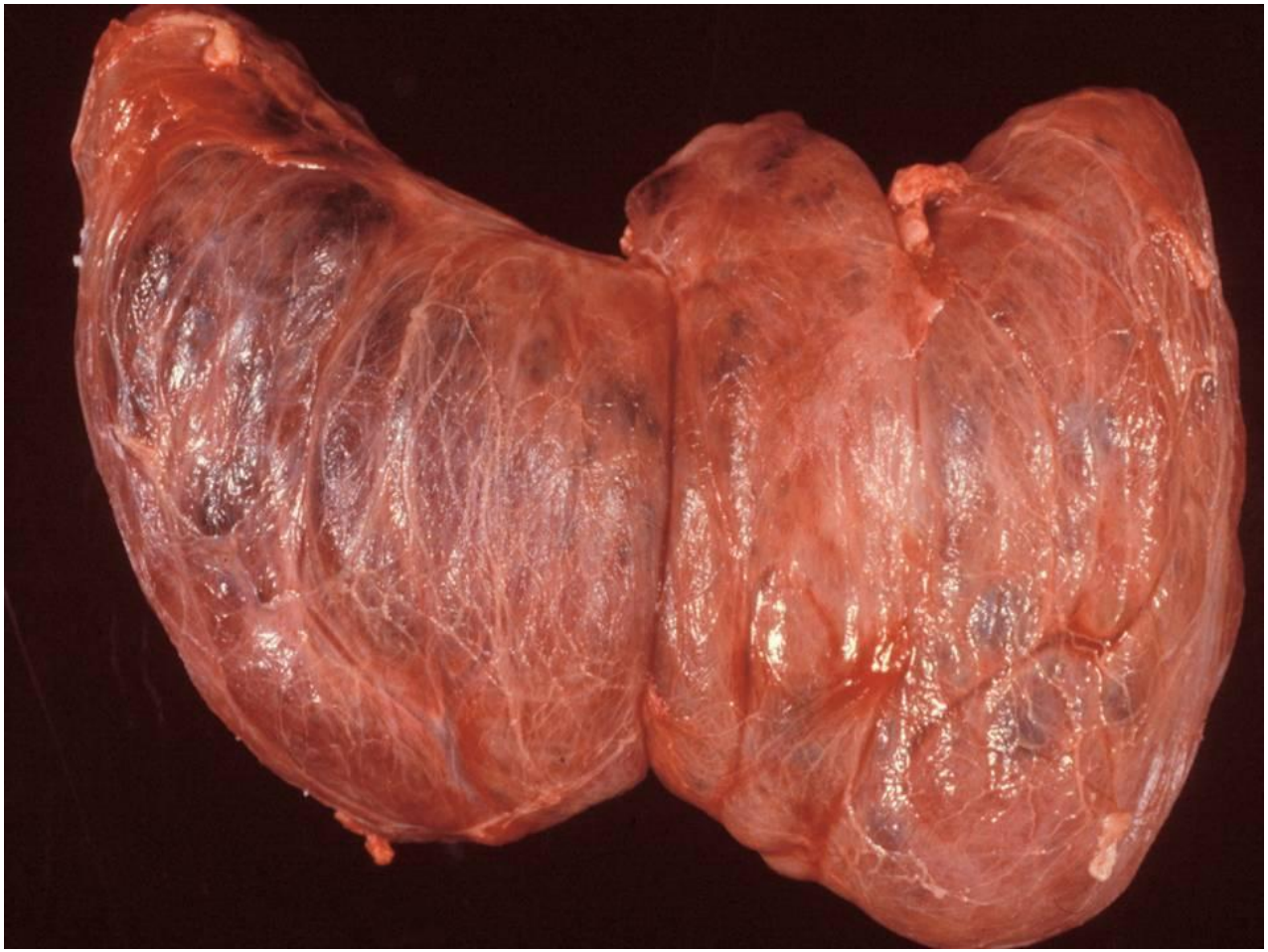
Case B



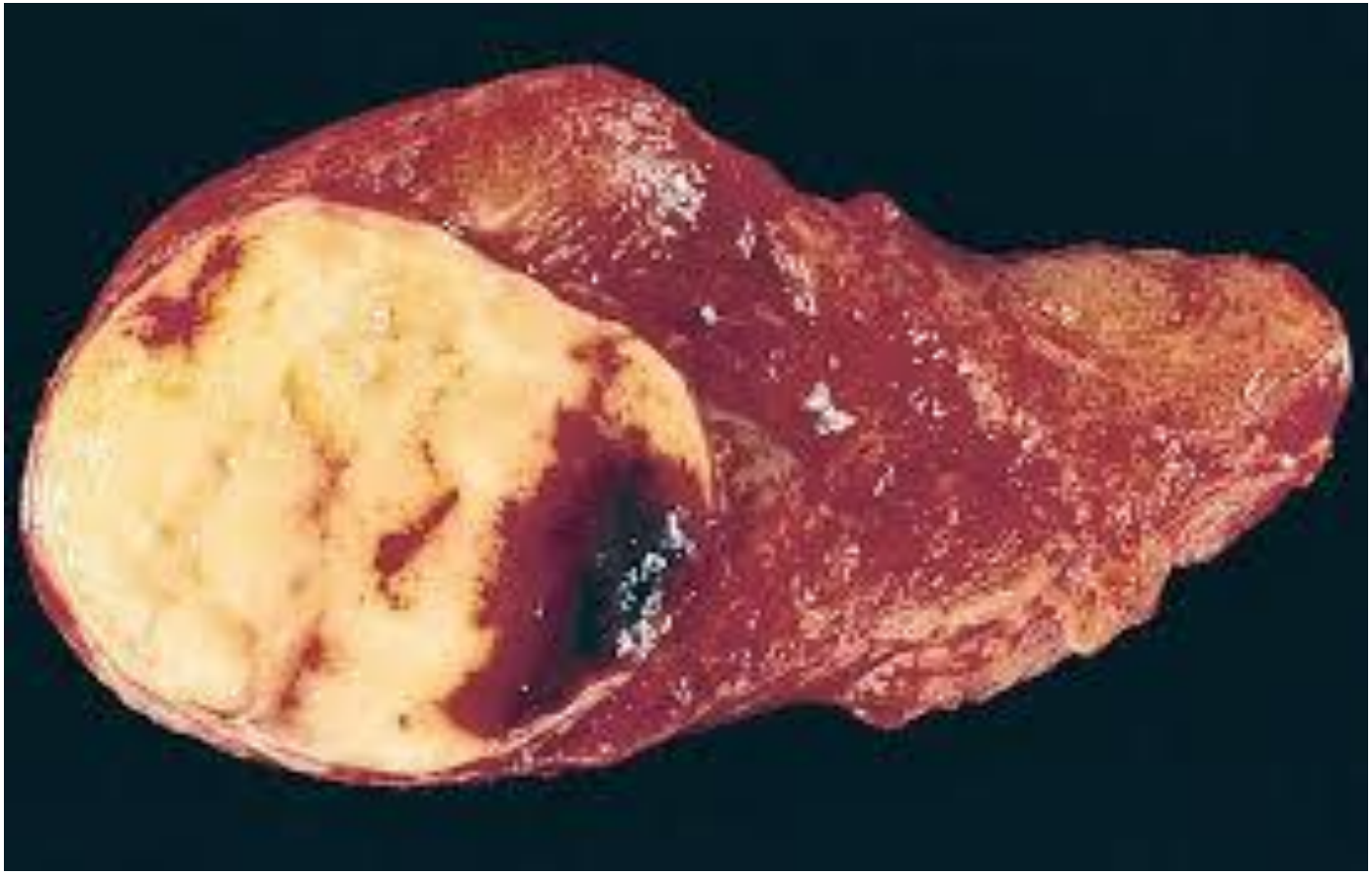
Case C



Case D



Case E

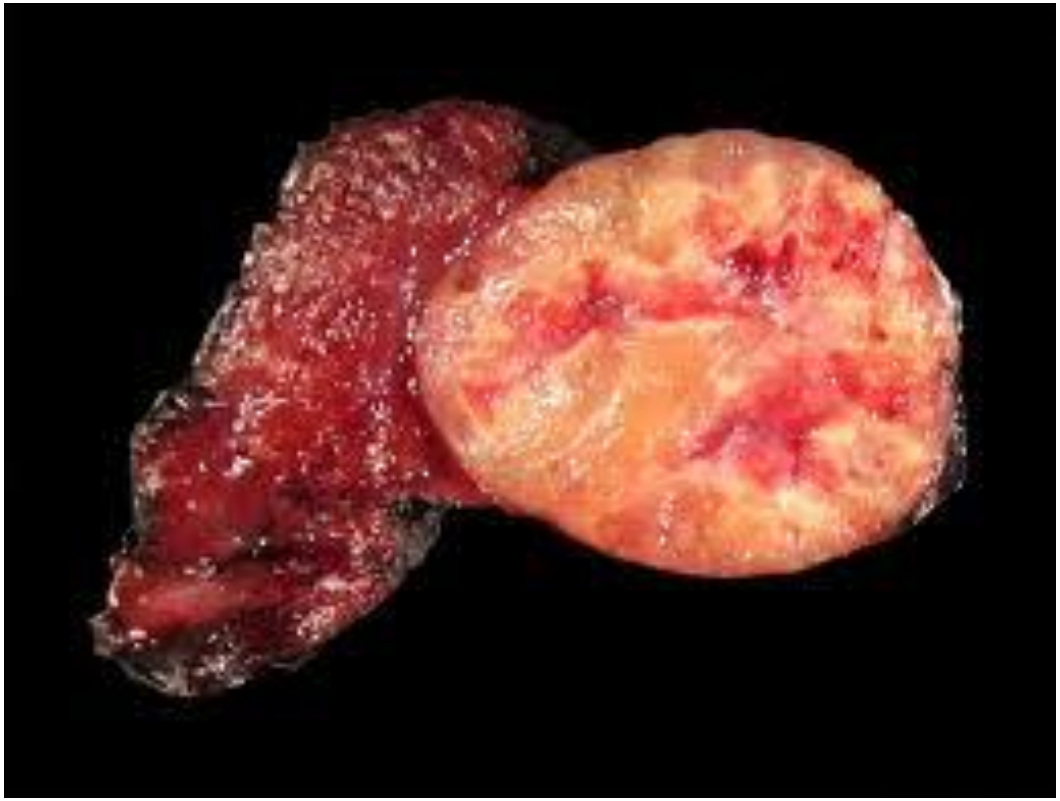


Answers

- A: multinodular.
- B and D: Diffuse
- C and E: single nodule.

Thyroid tumors

- Thyroid neoplasms present as single nodules



Thyroid tumors

- Tumors of the thyroid gland can be benign or malignant.
- They are usually solitary (single not multiple)
- Benign lesions in the thyroid are commoner than malignant ones.

Solitary thyroid nodules

- In clinical practice, if you see a patient with solitary nodule, your differential diagnosis will include neoplastic and non- neoplastic lesions such as:

a. Follicular adenomas
b. A dominant nodule in multinodular goiter
c. Simple cysts
d. foci of thyroiditis

- So: neoplasms usually present as single (solitary) nodules, but not every single nodule is neoplastic.

Neoplastic thyroid lesions

Benign: follicular adenoma and its variants (example: Hurthle cell adenoma, atypical adenoma)

Malignant:

1.papillary carcinoma

2. Follicular carcinoma

3. medullary carcinoma

4. Anaplatic carcinoma.

5. lymphomas

Follicular adenomas

- Are benign neoplasms derived from follicular epithelium.
- Usually solitary.
- The tumor is demarcated and compresses the adjacent thyroid parenchyma by a well-defined, intact capsule

Microscopic examination of follicular adenoma,

- The cells are arranged in follicles and its variants

a. Hurthle cell adenoma:

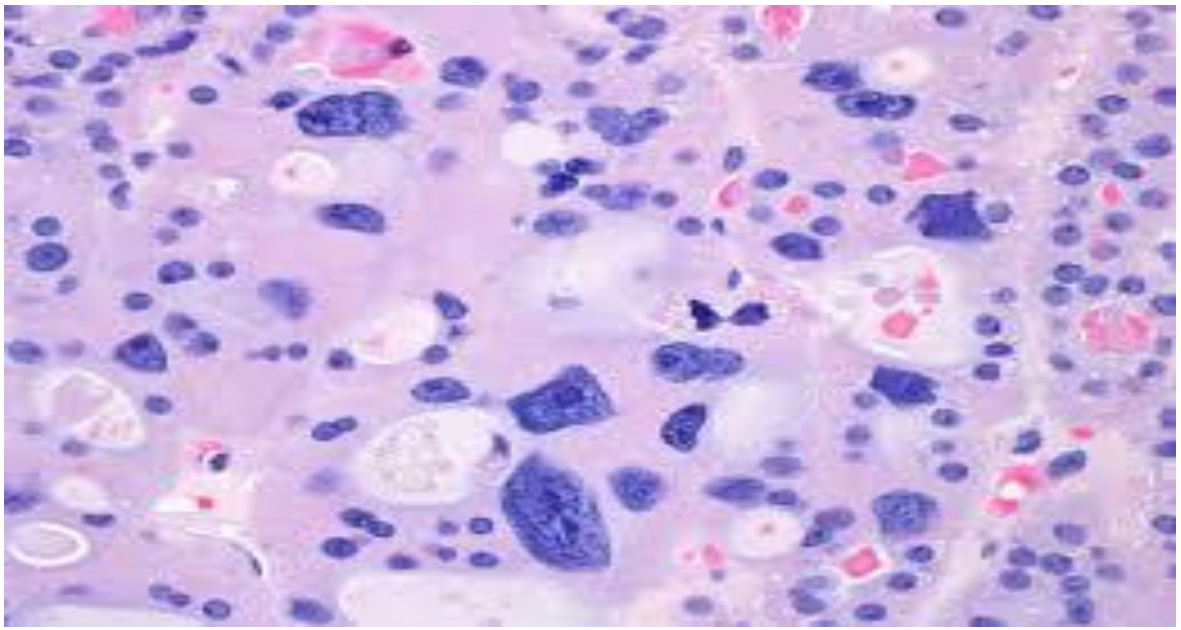
- The neoplastic cells show oxyphil or Hürthle cell change) and its behavior is not different from those of a conventional adenoma.

b. Atypical adenoma:

- The neoplastic cells exhibit focal nuclear atypia, (endocrine atypia);and these features do not constitute evidence of malignancy

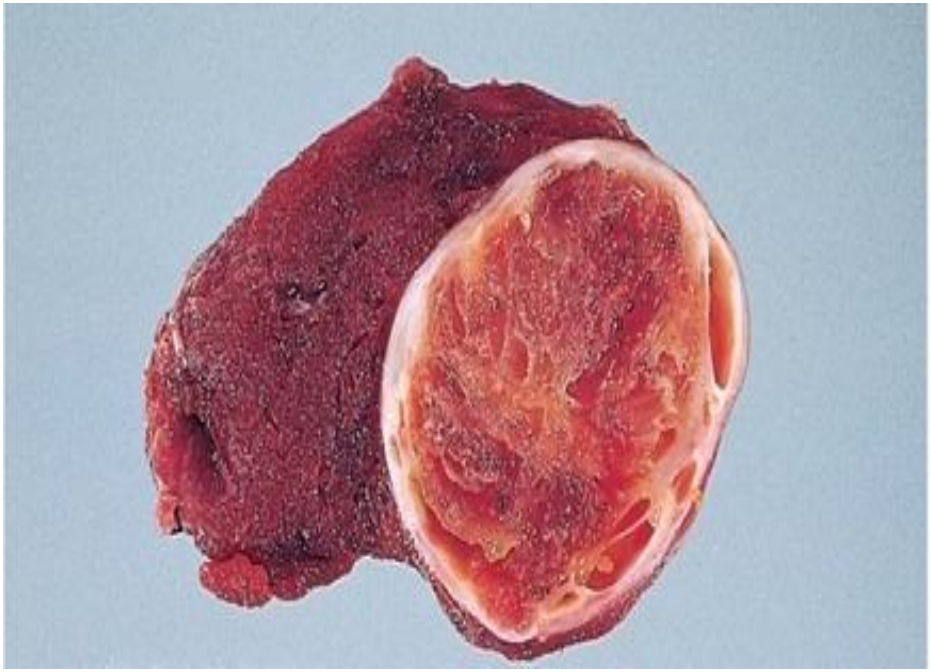
Endocrine atypia

- Note the large, hyperchromatic, pleomorphic cells. These are atypical and this atypia in endocrine glands doesn't necessarily mean malignancy.

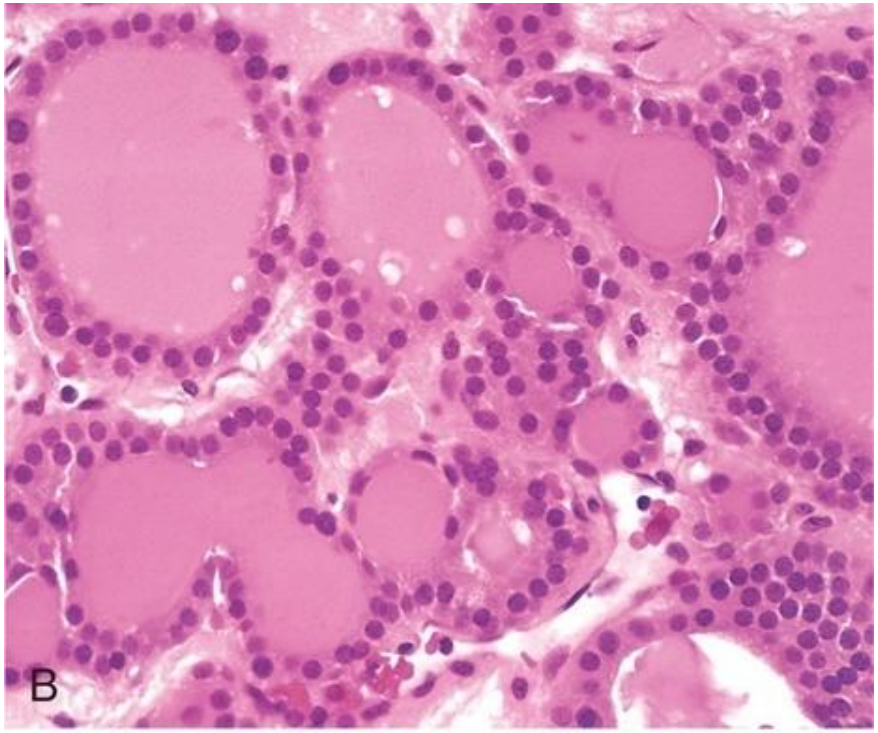


Follicular adenoma

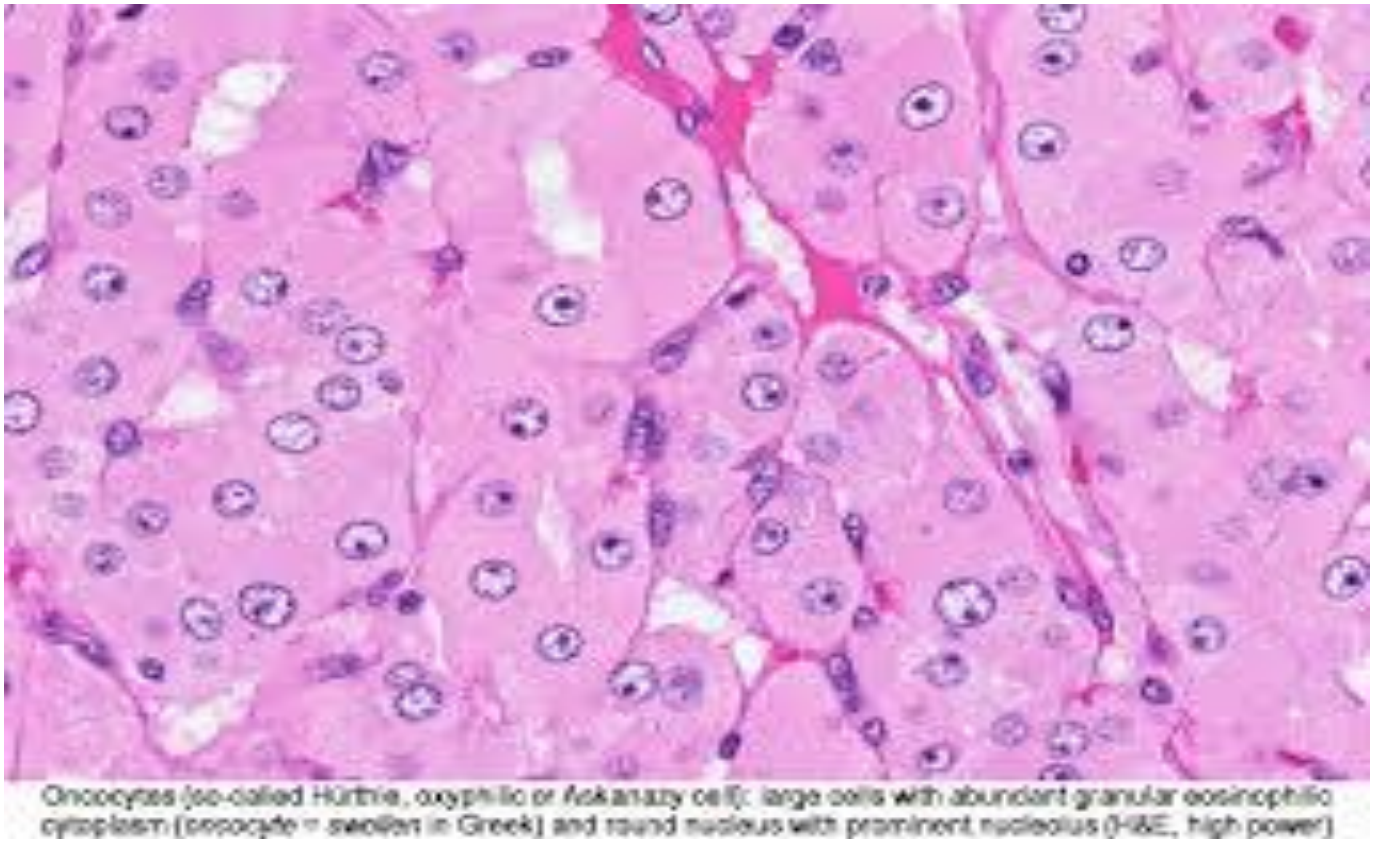
- Well demarcated, encapsulated nodules.



Micro: composed of follicles similar to the normal thyroid follicles.



Hurthle cell adenoma, cells are large with abundant eosinophilic cytoplasm.



- Behavior of thyroid adenomas :

a. Carry an excellent prognosis
b. Do not recur or metastasize
c. *Not* forerunners to carcinomas, i:e they are not premalignant.

Thyroid carcinoma

- Account for about 1.5% of all cancers
- A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years

-cases manifesting in childhood and late adult life are distributed equally between men and women

Main types

1. Papillary carcinoma (for more than 85% of cases)
2. Follicular carcinoma (5% to 15% of cases)
3. Anaplastic carcinoma (less than 5% of cases)
4. Medullary carcinoma (5% of cases

Papillary Carcinoma :

Is the most common form

- accounts for the majority of thyroid carcinomas associated with previous exposure to ionizing radiation.
- May occur at any age.

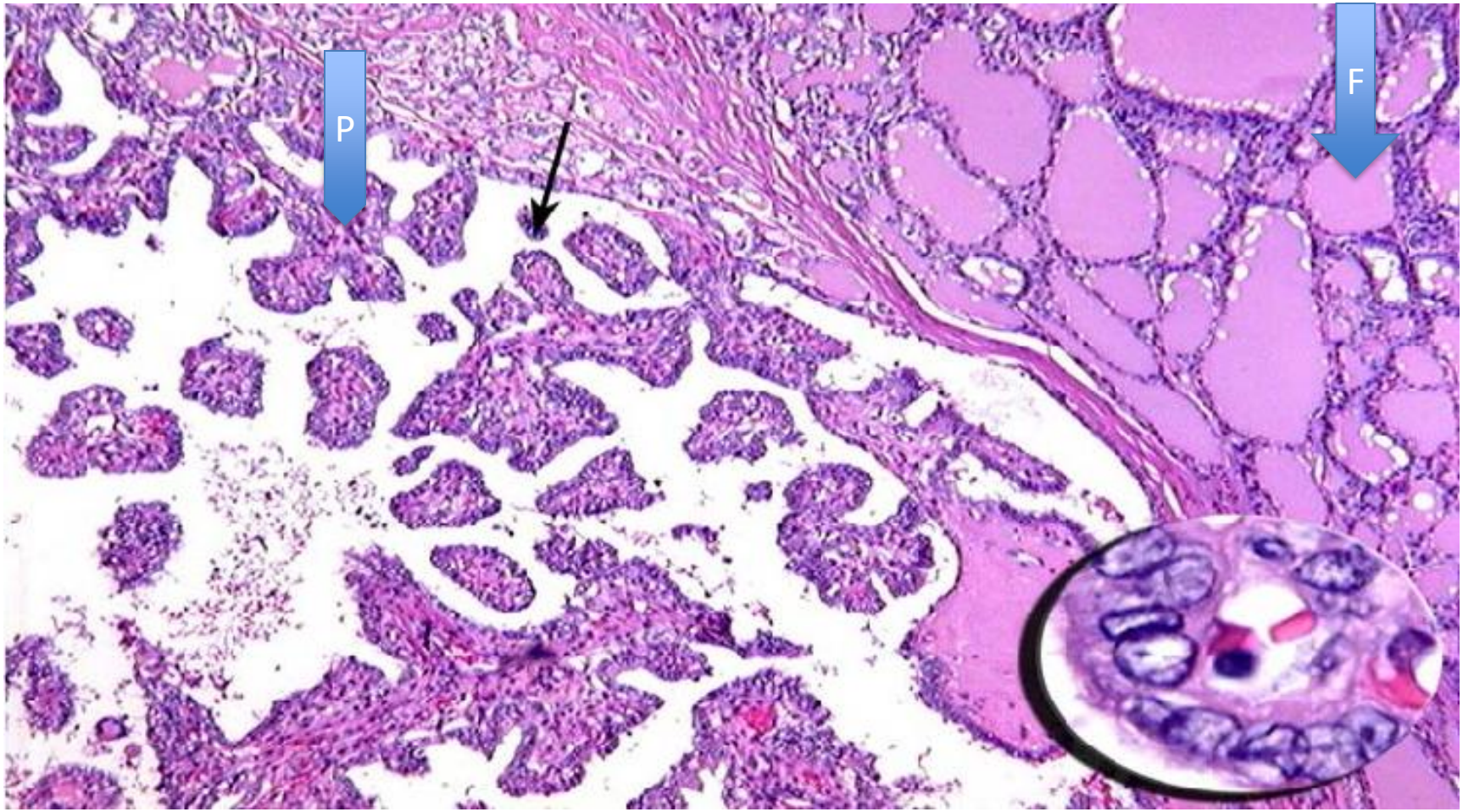
Gross: Either solitary or multifocal lesions

- note: papillary carcinoma can be multifocal.

Microscopic features of papillary carcinoma

- 1. the presence of papillae.
- 2. nuclear features
- 3. Concentrically calcified structures (psammoma bodies)

Papillae (P). Note the difference from the normal follicles (F)

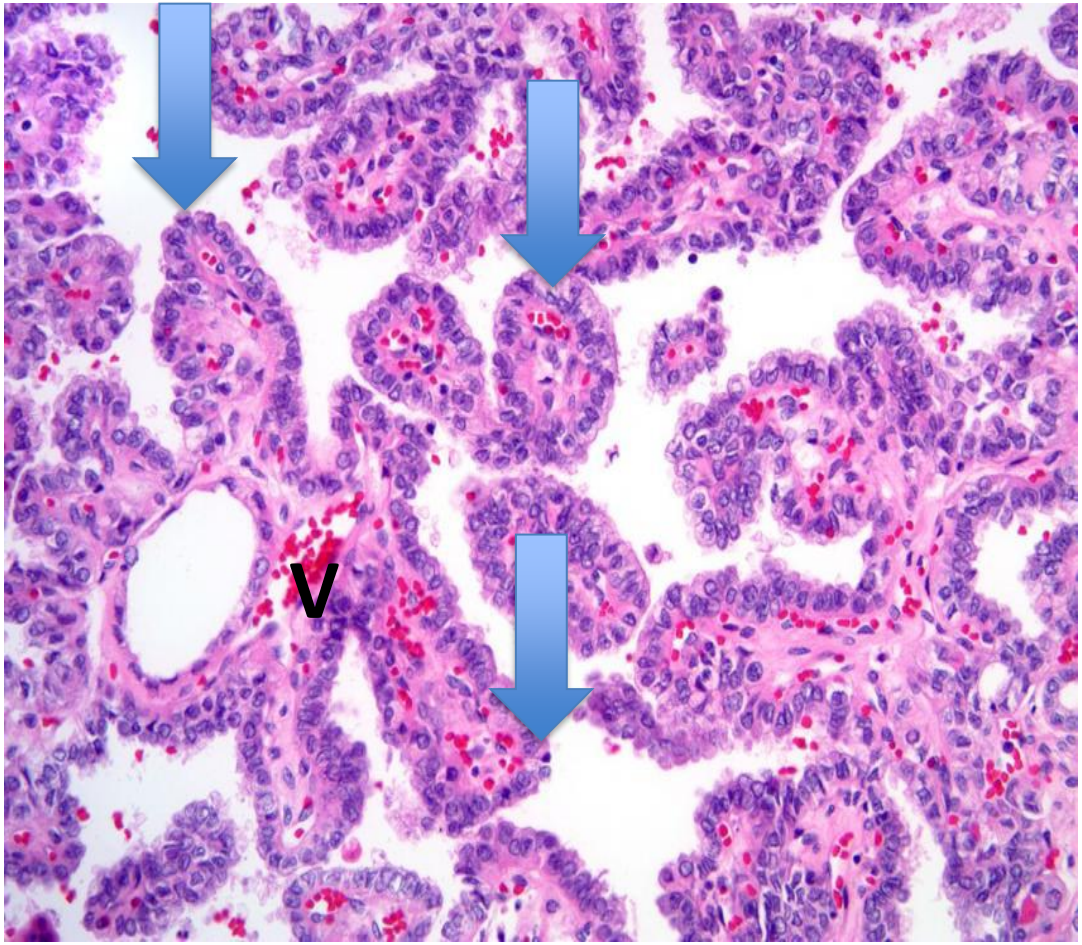


Papillae

-Papillae (arrows) are finger-like projections covered by epithelial cells (the blue dots around the papillae).

-The papillae have fibro-vascular cores (central region which is fibrous and contains blood vessels (V))

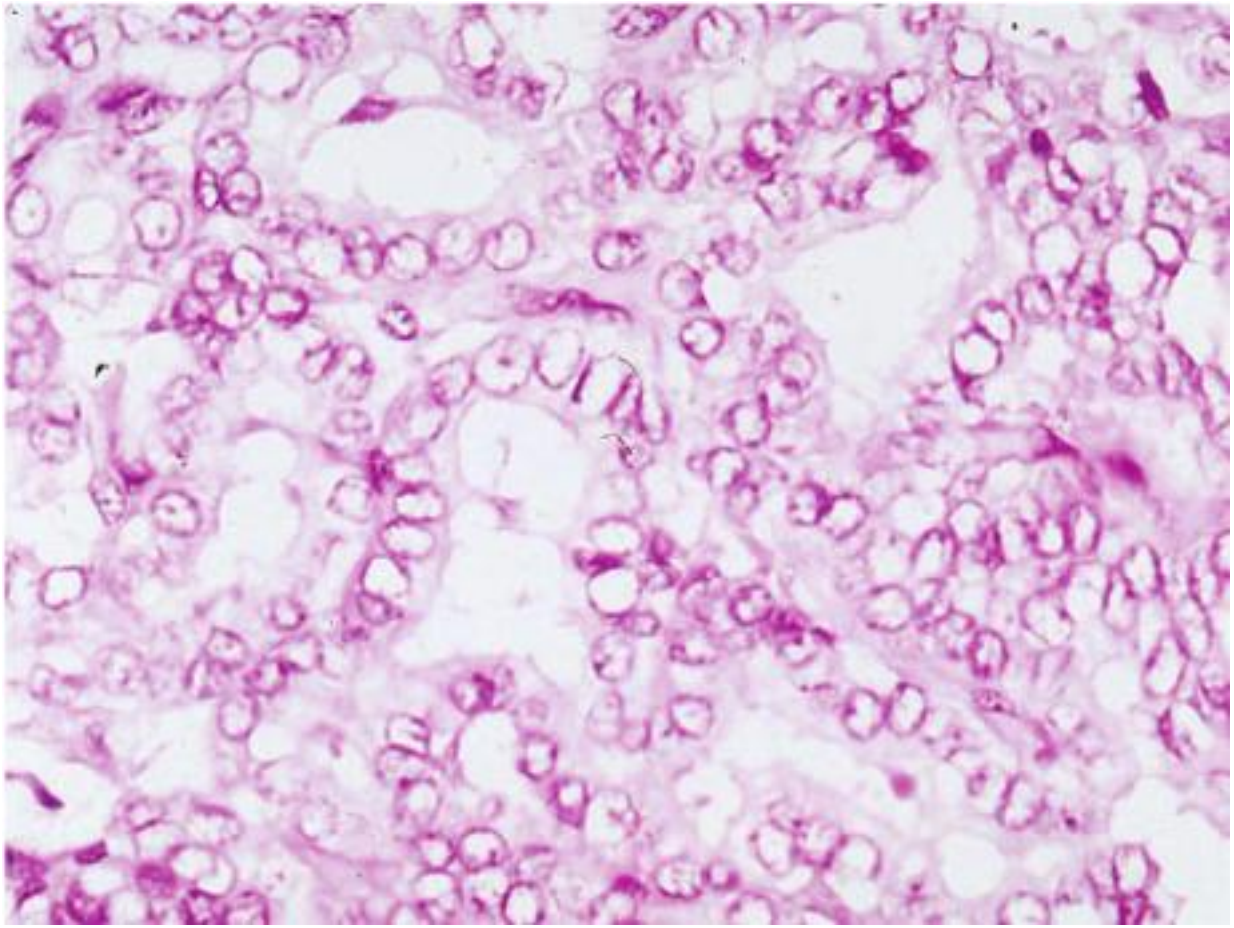
Note: all the red dots in the pic are red blood cells within the vessels.



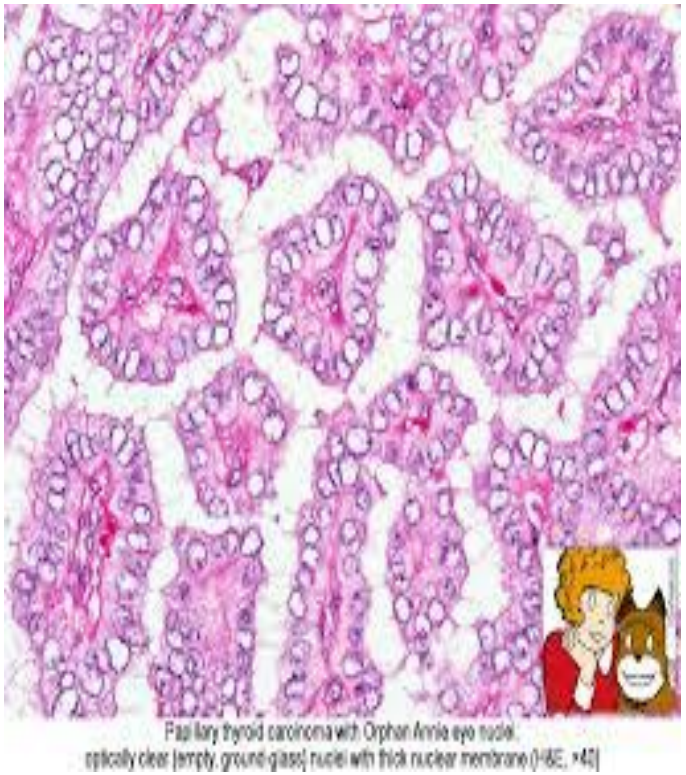
Nuclear features

1. optically clear nuclei, or "Orphan Annie eye" nuclei , seen on histological but not cytological preparations (formalin artefact)
2. Have invaginations of the cytoplasm to the nucleus (pseudoinclusions)
3. Grooves within nuclei: so the nucleus looks like a coffee bean.

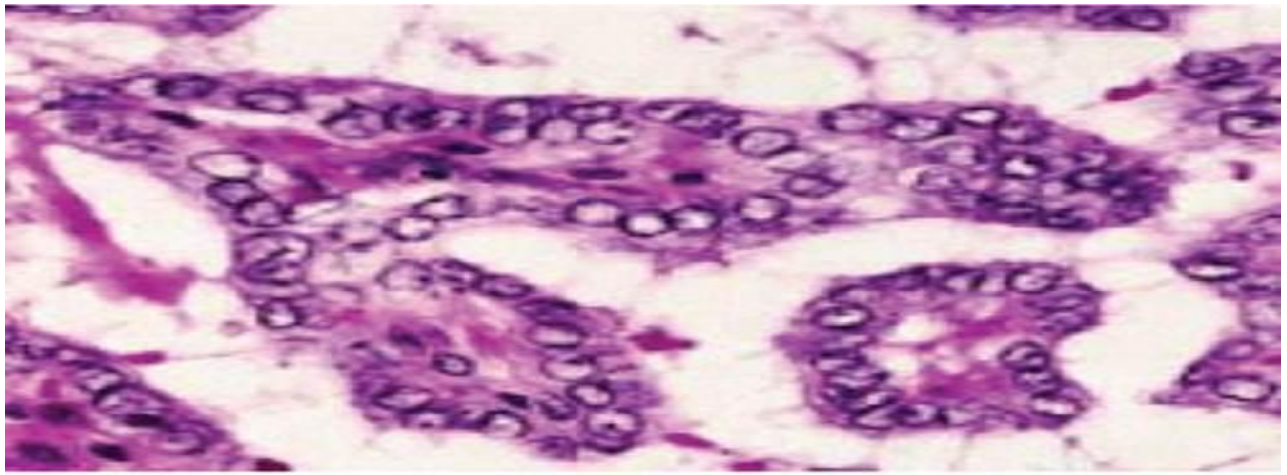
Clear nuclei: note the nuclei are white.



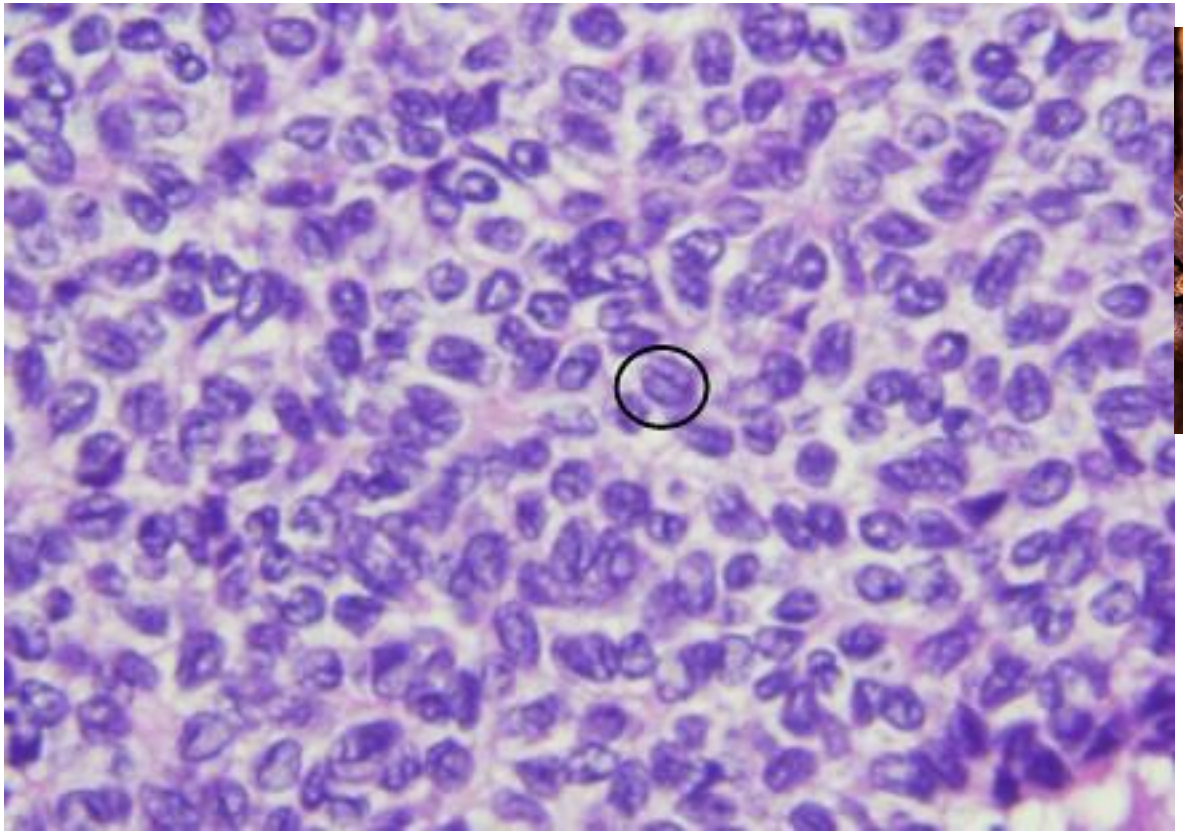
Orphan Annie eye! Because the nuclei are white and empty like Annie's character eyes!!



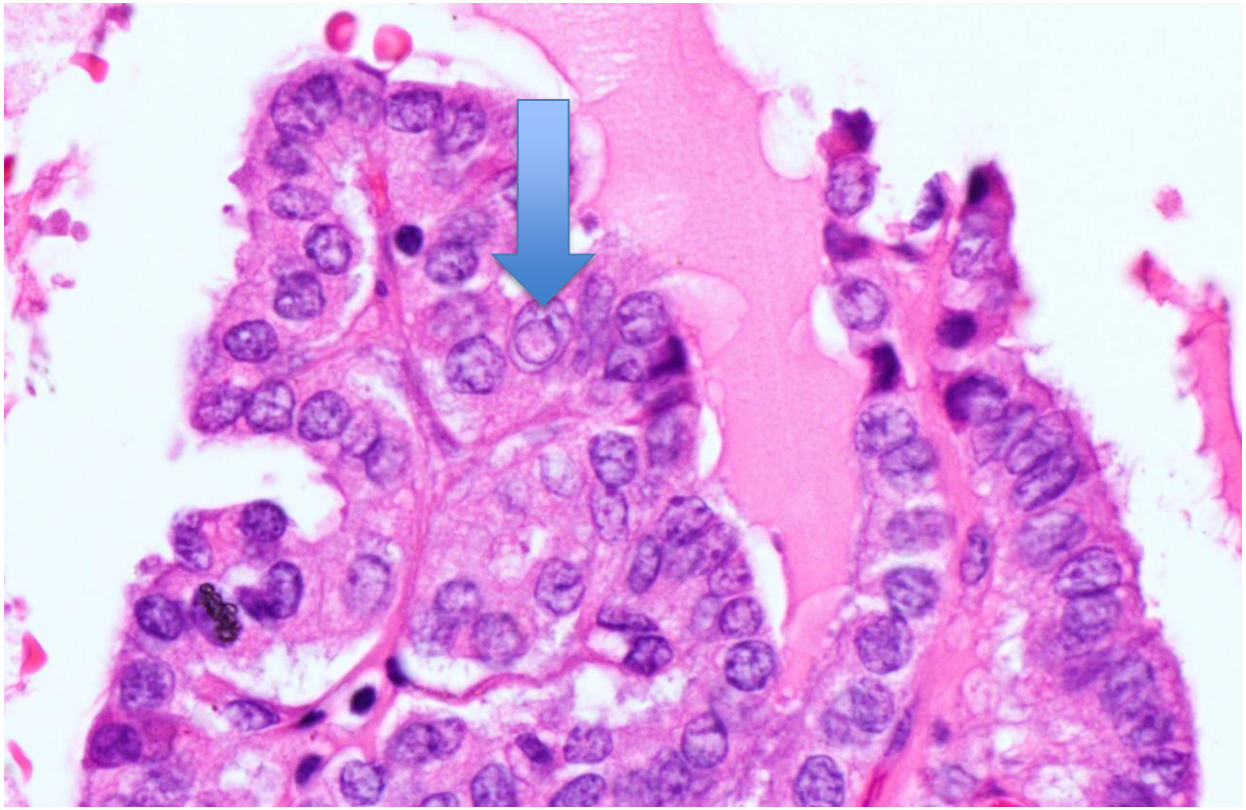
I know what you're thinking: pathological terms are funny.. You’re right



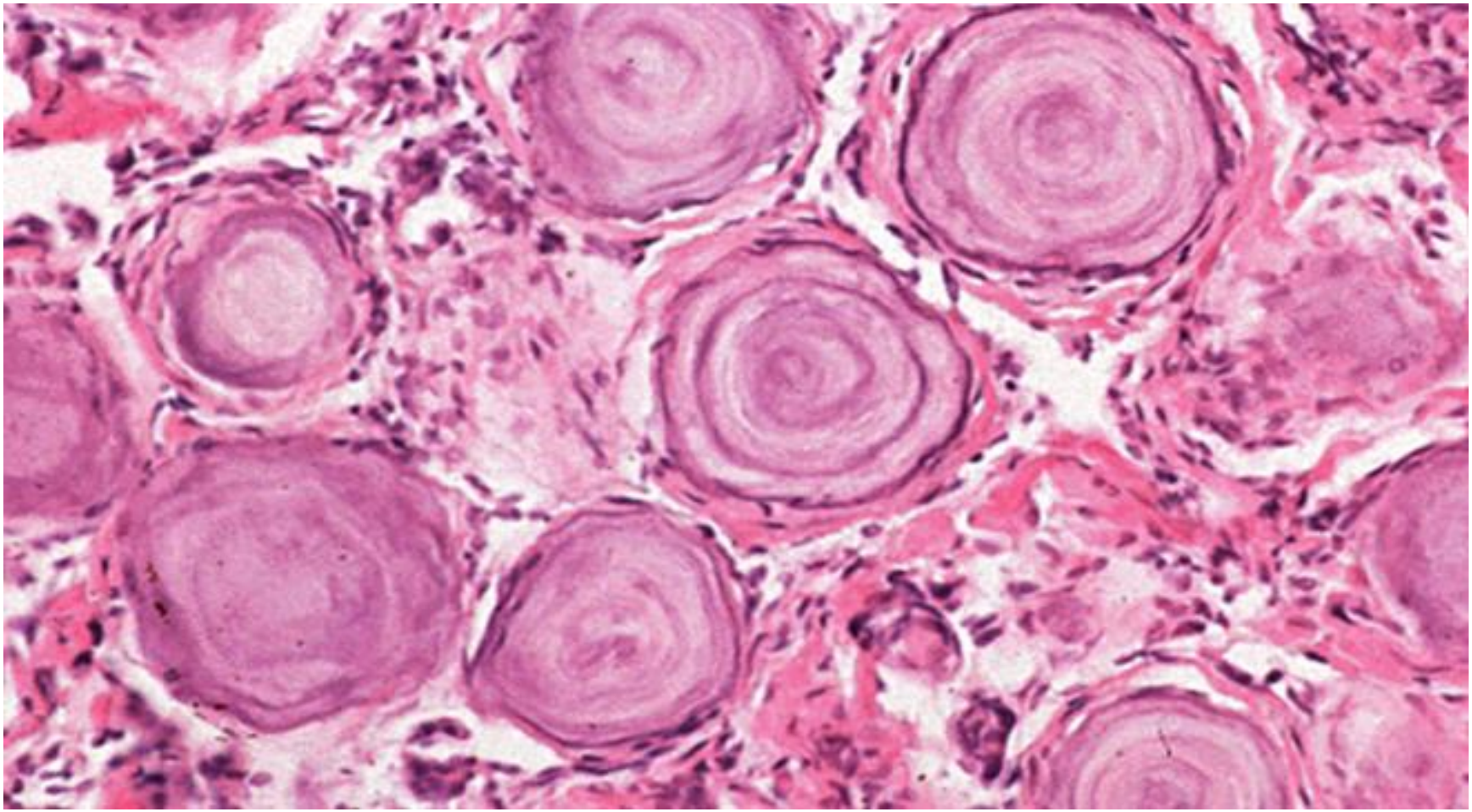
Nuclear grooves= coffee bean nuclei



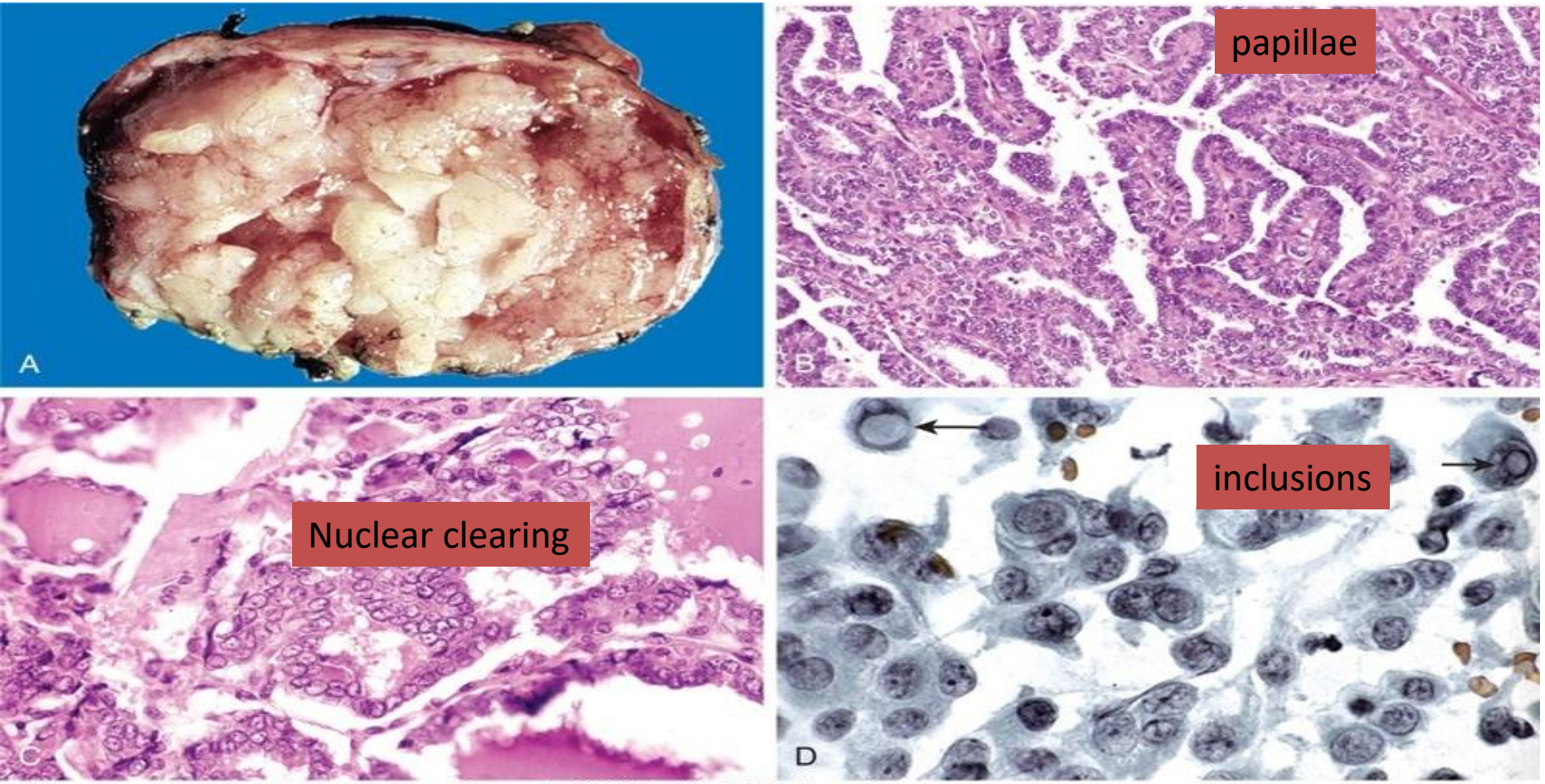
Nuclear inclusions



Psammoma bodies



Papillary carcinoma



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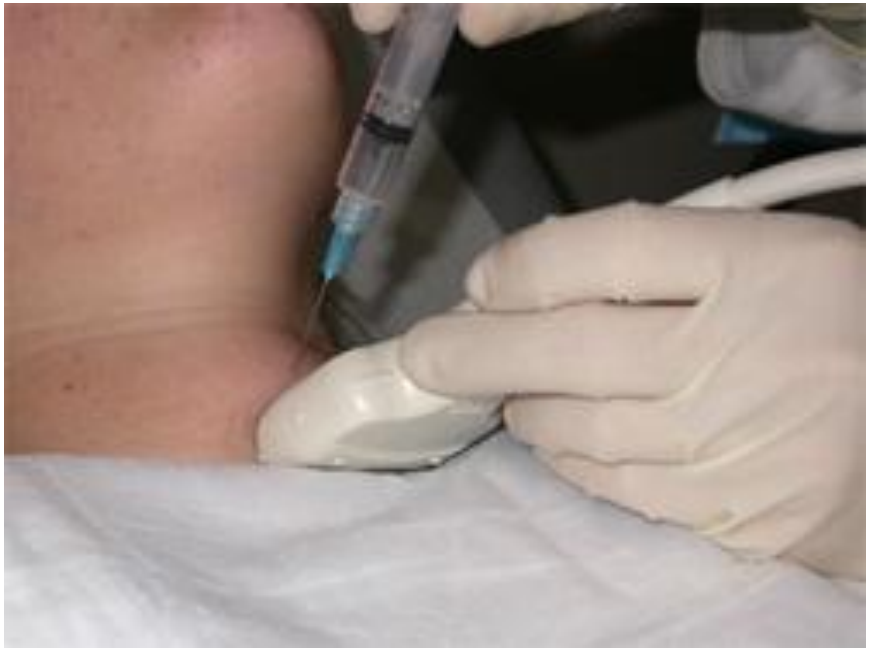
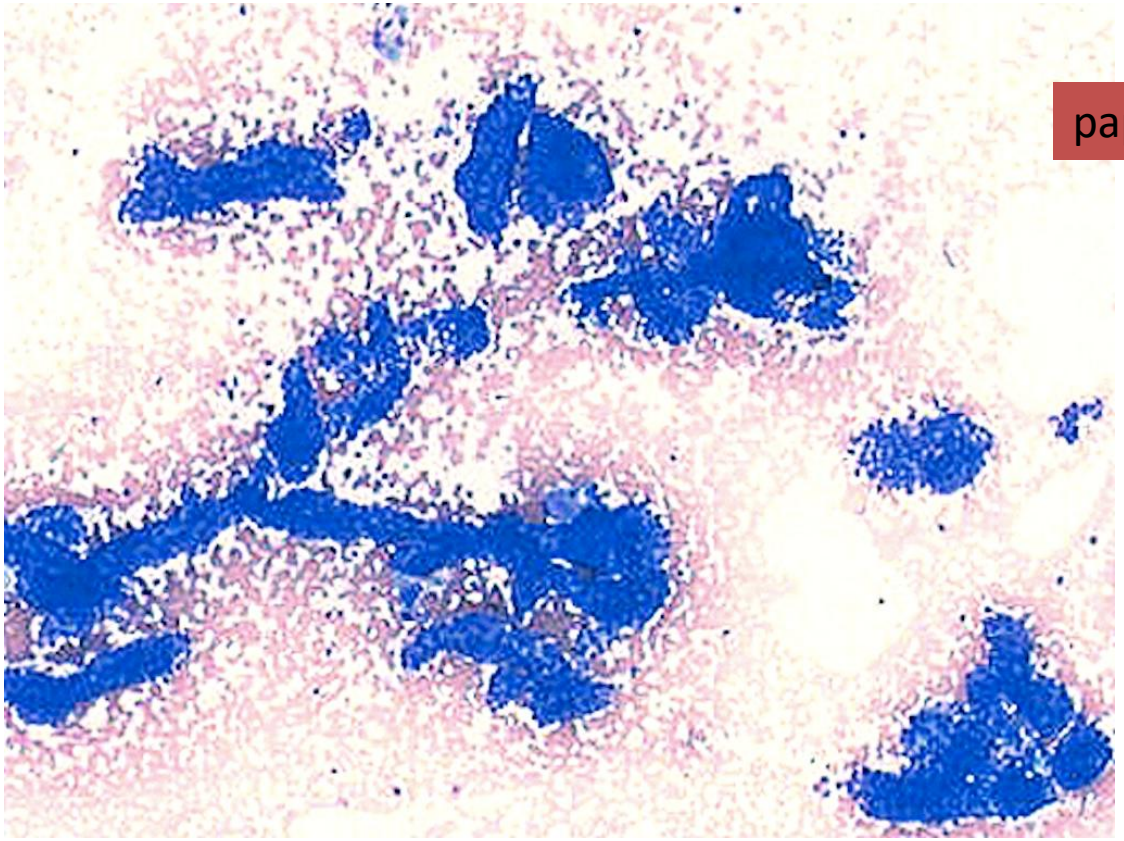
Papillary carcinoma can be diagnosed on FNA (fine needle aspiration)

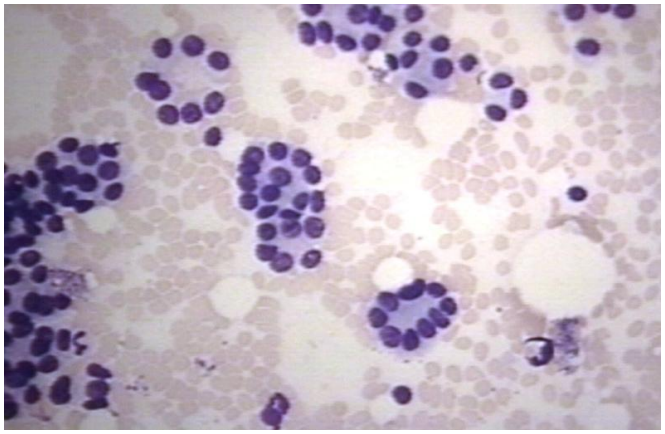


Papillae on FNA: compare to how rounded follicles are seen on the bottom pic

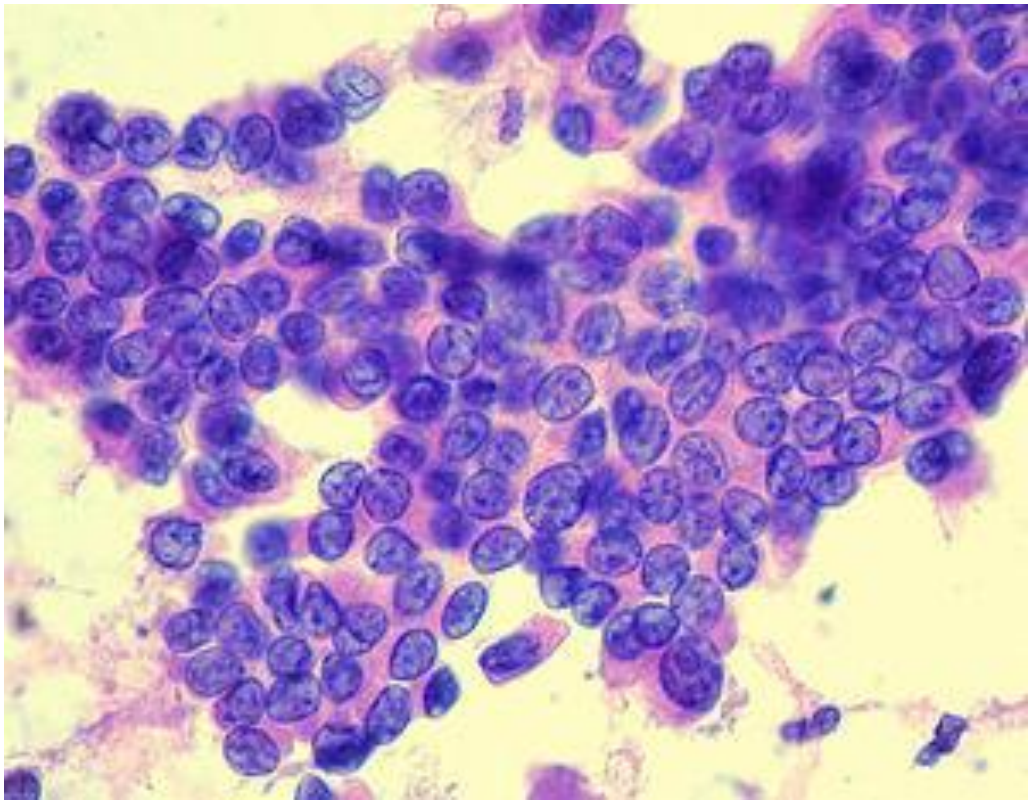


papillae

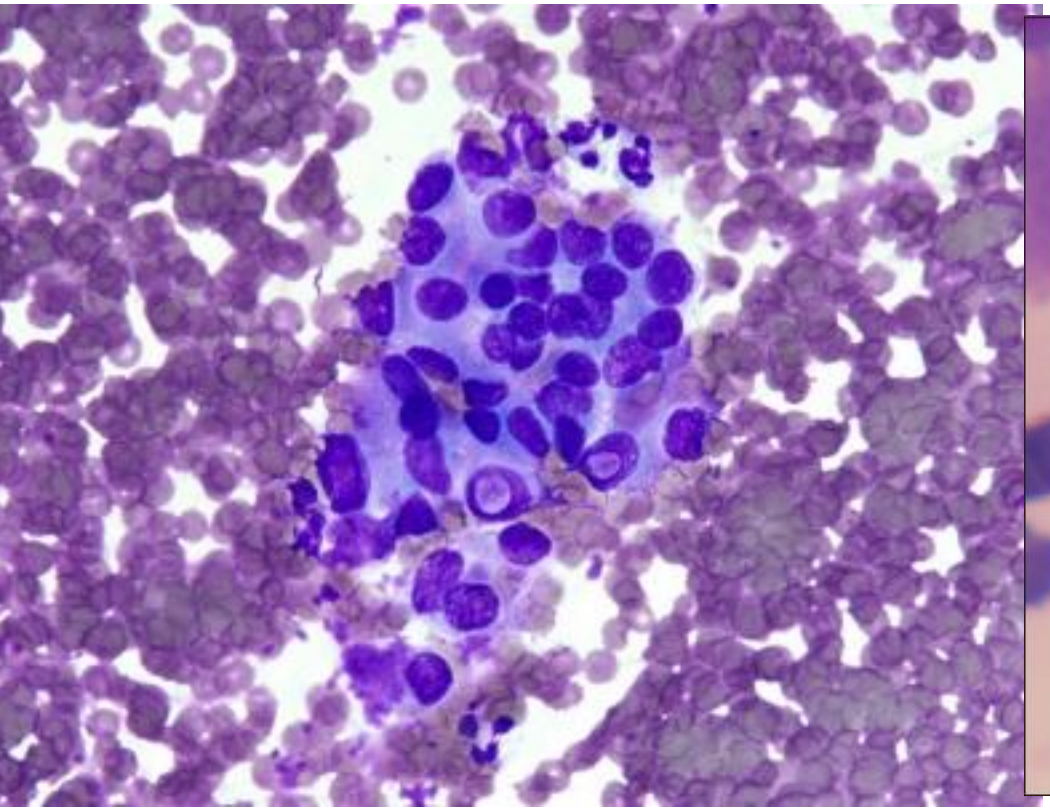
follicles

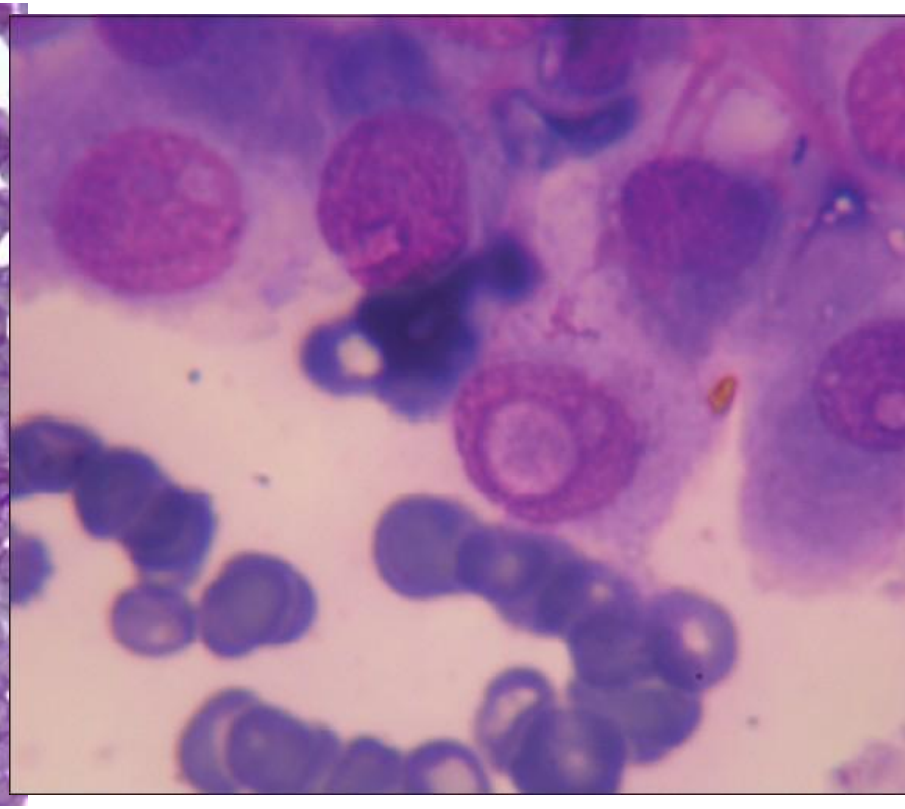


Grooves seen on FNA

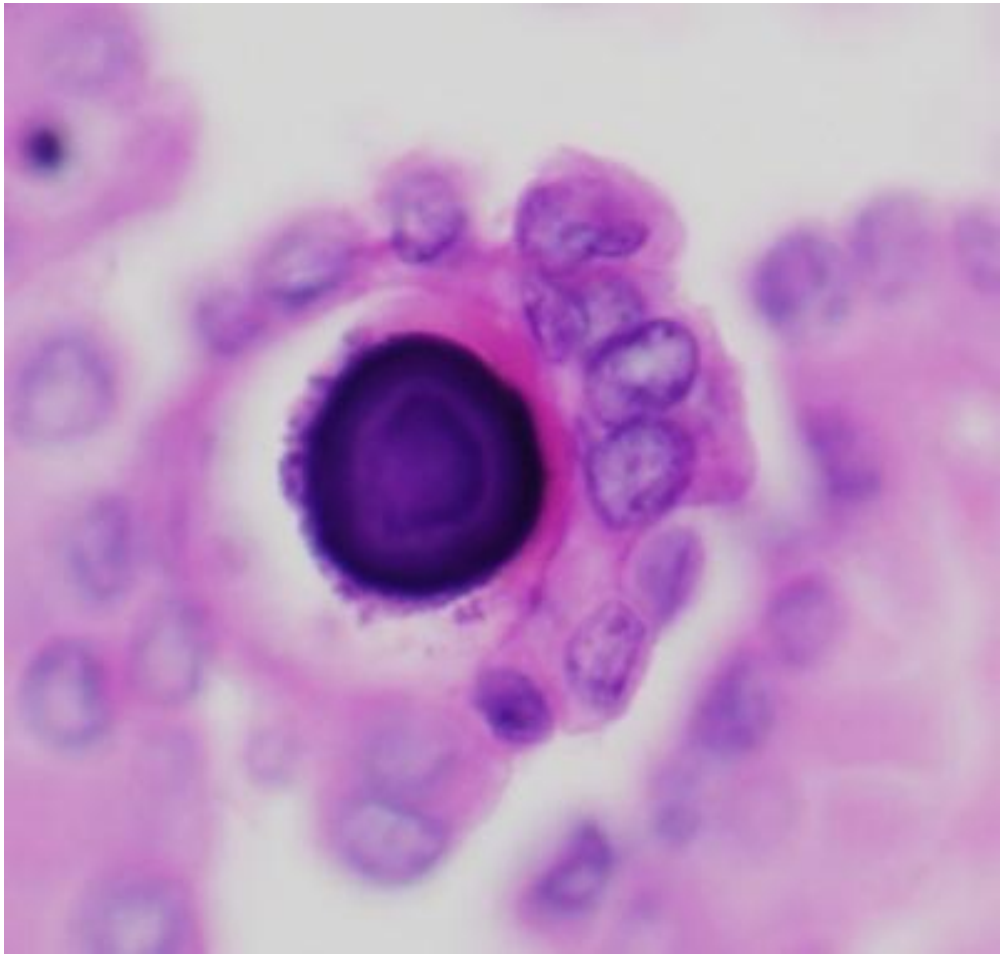


Inclusions seen on FNA





Psammoma bodies can be seen on GNA



Clinical Features of papillary carcinomas

a. Are nonfunctional tumors that manifest as painless masses in the neck, either within the thyroid or as metastasis in a cervical lymph node

b. Are indolent lesions, with 10-year survival rates of 95%.

c. The presence of isolated cervical nodal metastases does not have influence on good prognosis of these lesions.

d. In a minority of patients, hematogenous metastases are present at the time of diagnosis, most commonly to lung.

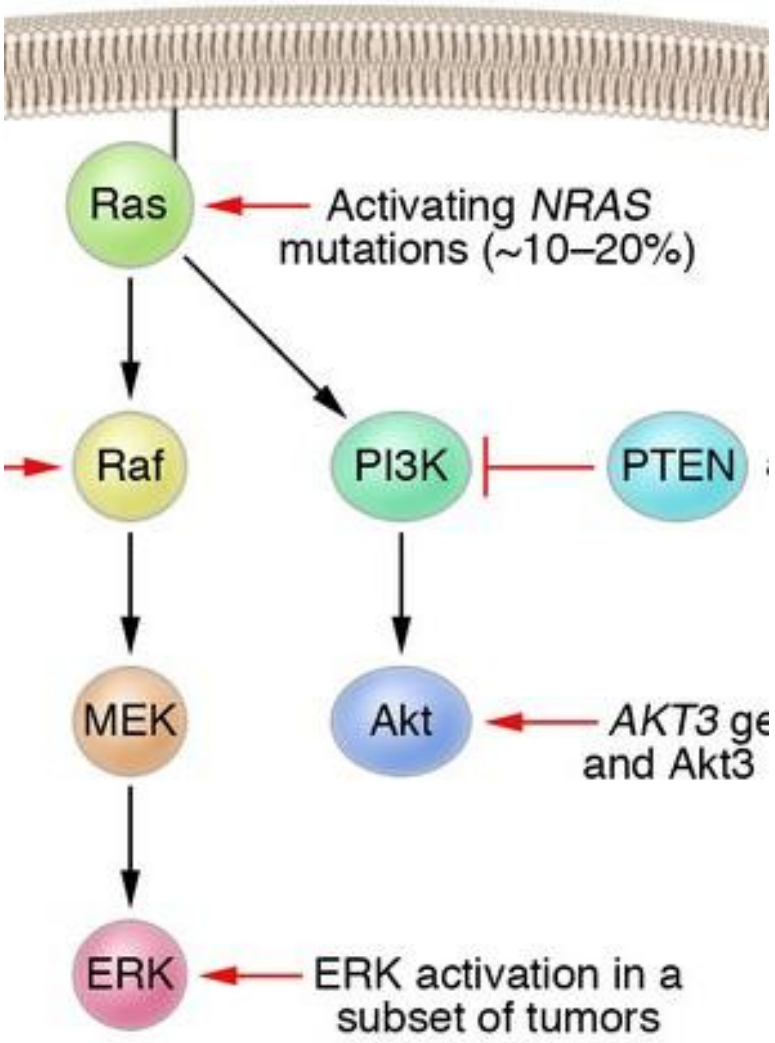
Genetic factors related to papillary carcinoma

- Mainly 2 oncogenes are involved:
- 1. BRAF amplification. (protein in the ras pathway)
- 2. RET gene rearrangement resulting in a novel protein kinase.

Remember that RAS is the most commonly mutated oncogene.

RAS acts via second messeanges .. RAF is one of them

BRAF (of the RAF family genes) is an oncogene in the RAS pathway.



RET rearrangement= translocation

- The *RET* gene is not normally expressed in follicular cells but in papillary cancers, chromosomal rearrangements place the tyrosine kinase domain of *RET* resulting in a novel kinase .
- RET rearrangement is present in 20% to 40% of papillary thyroid cancers.

Note: RET rearrangements and *BRAF* point mutations are not observed in follicular adenomas or carcinomas.

Follicular Carcinoma :

-- More common in women and in areas with dietary iodine deficiency .

- The peak incidence between the ages of 40 and 60 years

On microscopic examination,

- Are composed of fairly uniform cells forming small follicles,
- In other cases, follicular differentiation is less apparent
- It may be

a. widely invasive, infiltrating the thyroid parenchyma and extrathyroidal soft tissues, or

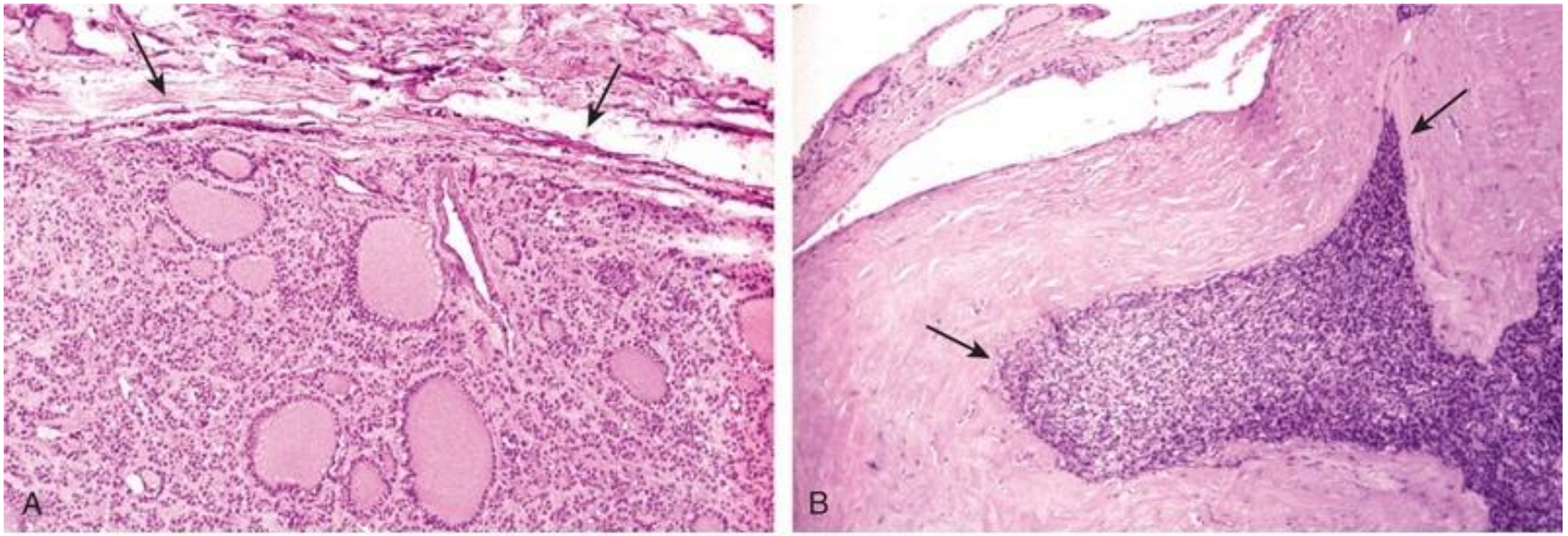
b. Minimally invasive that may be impossible to distinguish from follicular adenomas on gross examination and the .

- requires extensive histologic sampling to exclude capsular and/or vascular invasion

Clinical Features

- Manifest most frequently as solitary *cold thyroid nodules.*
- Tend to metastasize through the bloodstream (*hematogenous dissemination*) to lungs, bone, and liver.
- Regional nodal metastases are uncommon .
- As many as half of patients with widely invasive carcinomas die from their disease within 10 years, while less than 10% of patients with minimally invasive follicular carcinomas die within the same time span.

Follicular carcinoma



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GENETIC FACTORS

Follicular thyroid carcinomas:

a. activation of *RAS*

b. Loss-of-function mutations of *PTEN*, a suppressor gene

c. (2;3) translocation,

3. Anaplastic Carcinoma

- Are undifferentiated tumors of the thyroid epithelium,
- The mean age of 65 years.
- They are aggressive, with a mortality rate of 100%.
- Approximately a quarter of patients have a past history a well-differentiated carcinoma, and a 1/4th harbor a well-differentiated tumor in the resected specimen.
- Metastases to distant sites are common, but **death occurs in less than 1 year as a result of aggressive local growth which compromise of vital structures in the neck.**

GENETIC FACTORS

Anaplastic carcinomas:

Inactivation of *TP53*, restricted to anaplastic carcinomas and may also relate to their aggressive behavior

4. Medullary Carcinoma

- Arises from C cells.

- neuroendocrine neoplasms.
- Secrete calcitonin, the measurement of which plays an important role in the diagnosis and postoperative follow-up evaluation of patients.

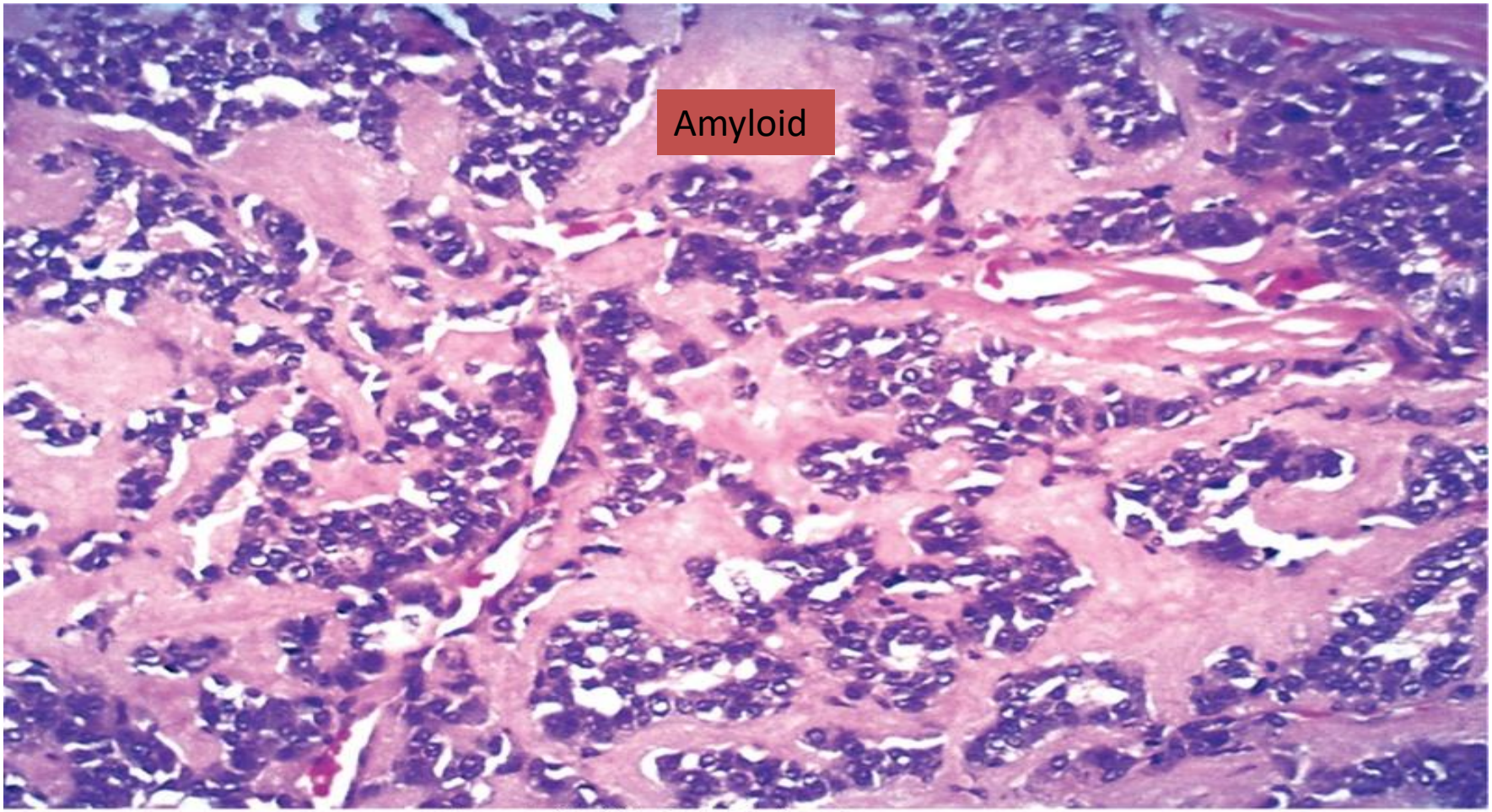
- Are sporadic in about 70% of cases and the remaining 30% are *familial* cases

Note: Both familial and sporadic forms demonstrate activating *RET* mutations.

- Because medullary carcinoma secrete calcitonin; this calcitonin can accumulate and form amyloid protein.

- Amyloid: is several, chemically different proteins that share similar physical characteristics.. They can accumulate and form pink material called amyloid.. See next pic.

Medullary carcinoma



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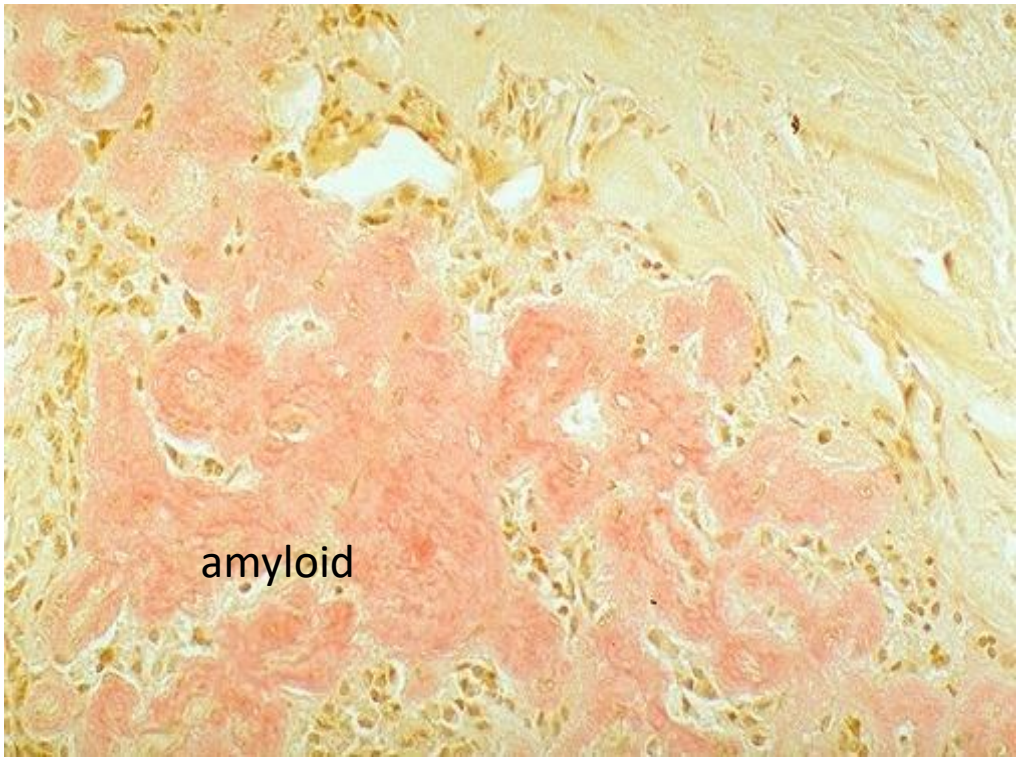
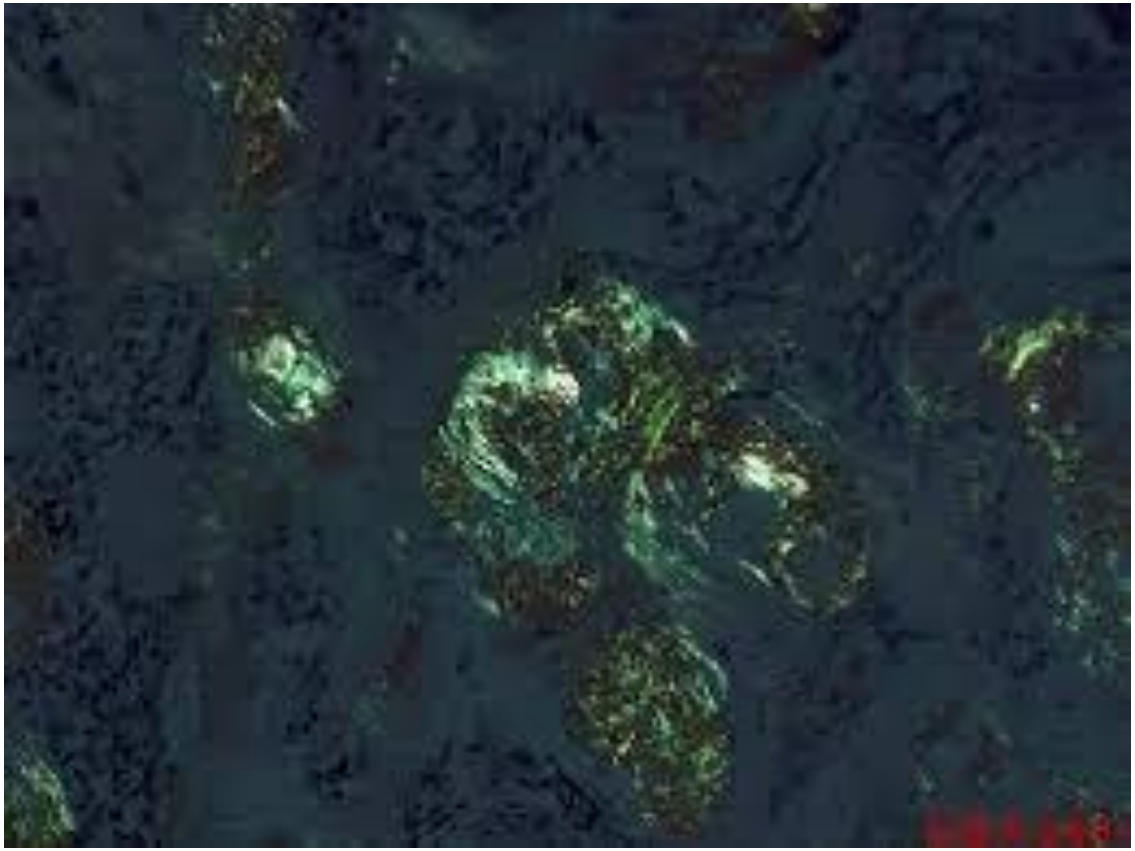
Amyloid stains with Congo red stain



With polarized light, amyloid gives this apple green color when stained with congo red



Thyroid lymphoma

- Thyroid lymphoma is a rare thyroid tumor.
- Most are non-Hodgkin B cell lymphomas
- most often affects women over 60 with Hashimoto's thyroiditis.
- Key features include a fast-growing neck mass and difficulty swallowing


Thank you!