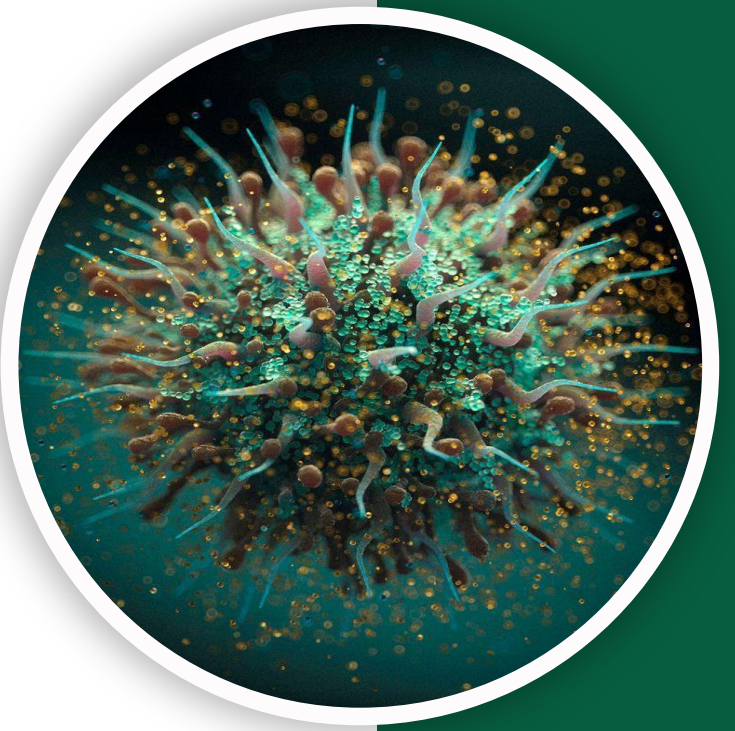
بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Pathology | FINAL #

Thyroid Gland Pt.2



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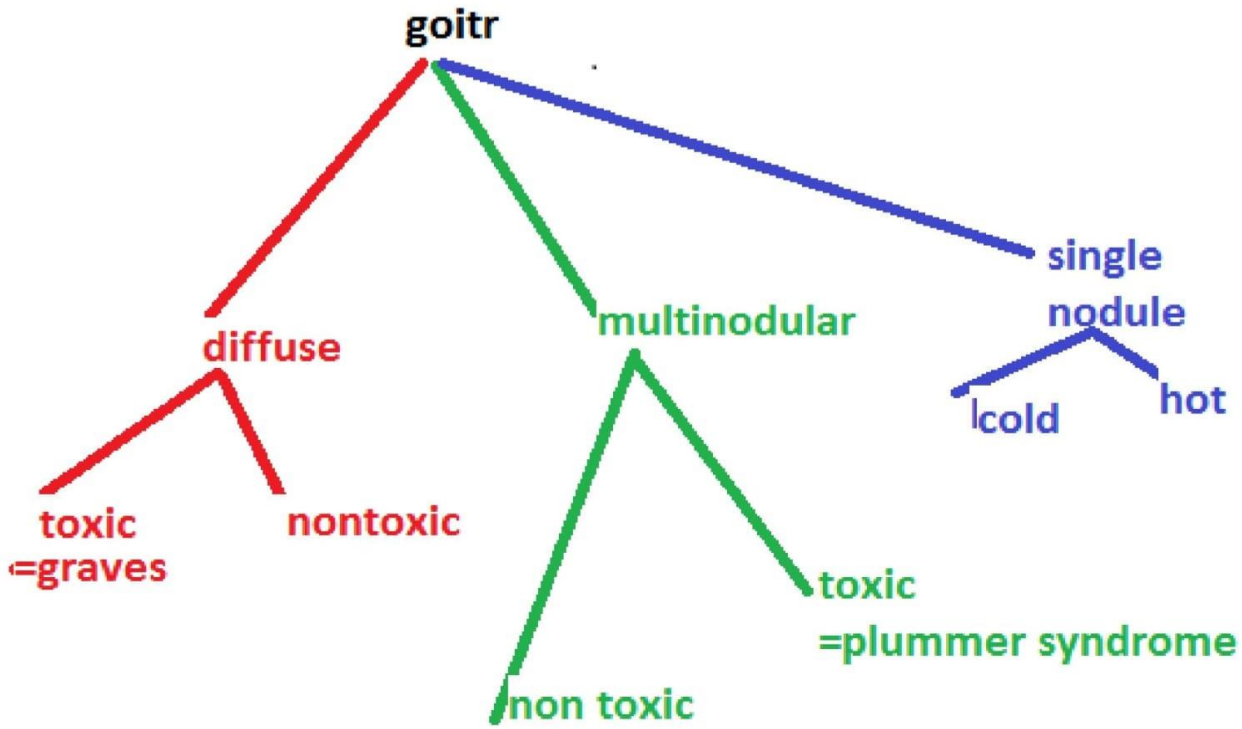
Ibrahim Alnajjar

Endocrine system
Thyroid gland part 2

Dr.Heyam Awad

MD, FRCPath

Goiter



Simple diffuse and simple multinodular diseases are caused by iodide deficiency ---> deficiency in T3 & T4

----> high TSH ---> hypertrophy and hyperplasia in the thyroid gland

Firstly, the enlargement is diffuse then it will be multinodular

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 T4 .
- 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.

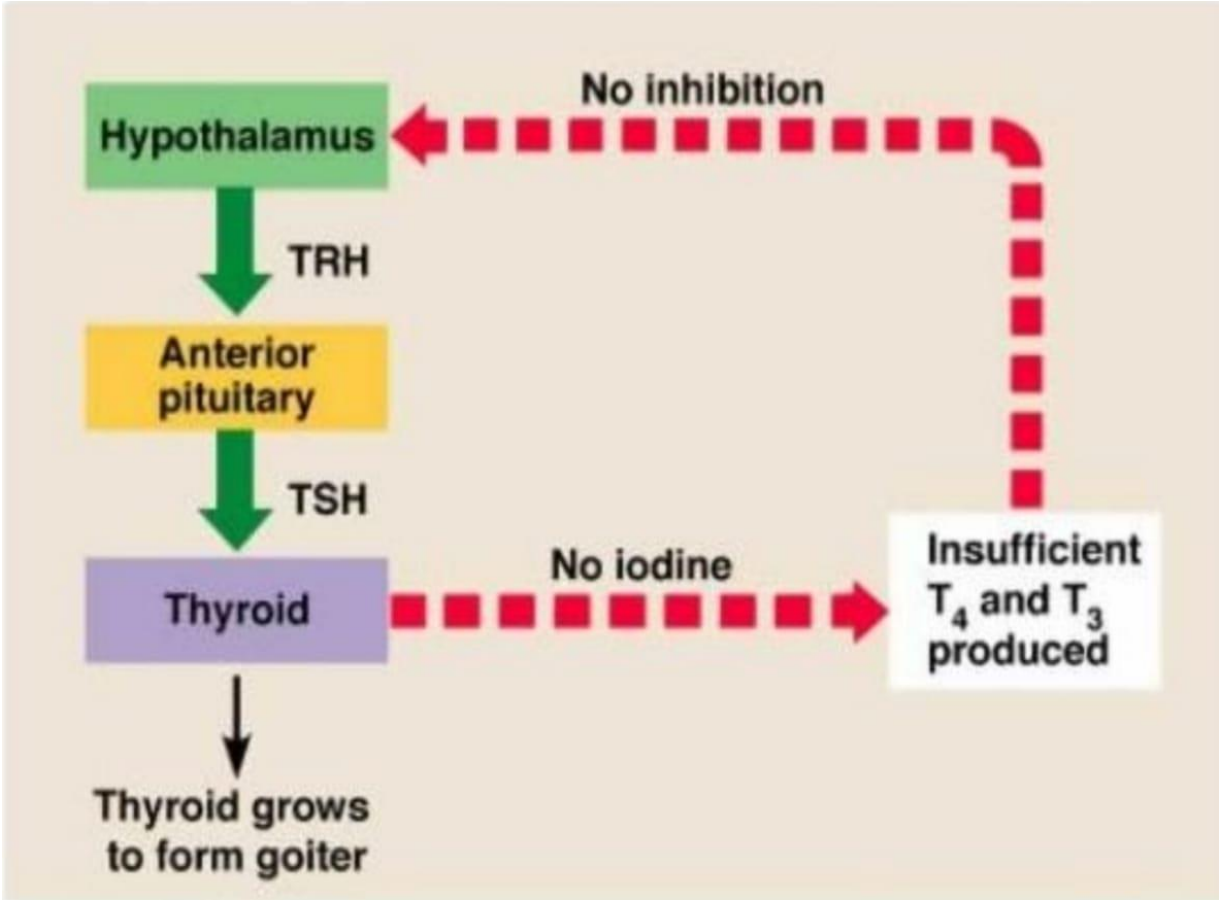
On microscopic examination,

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).

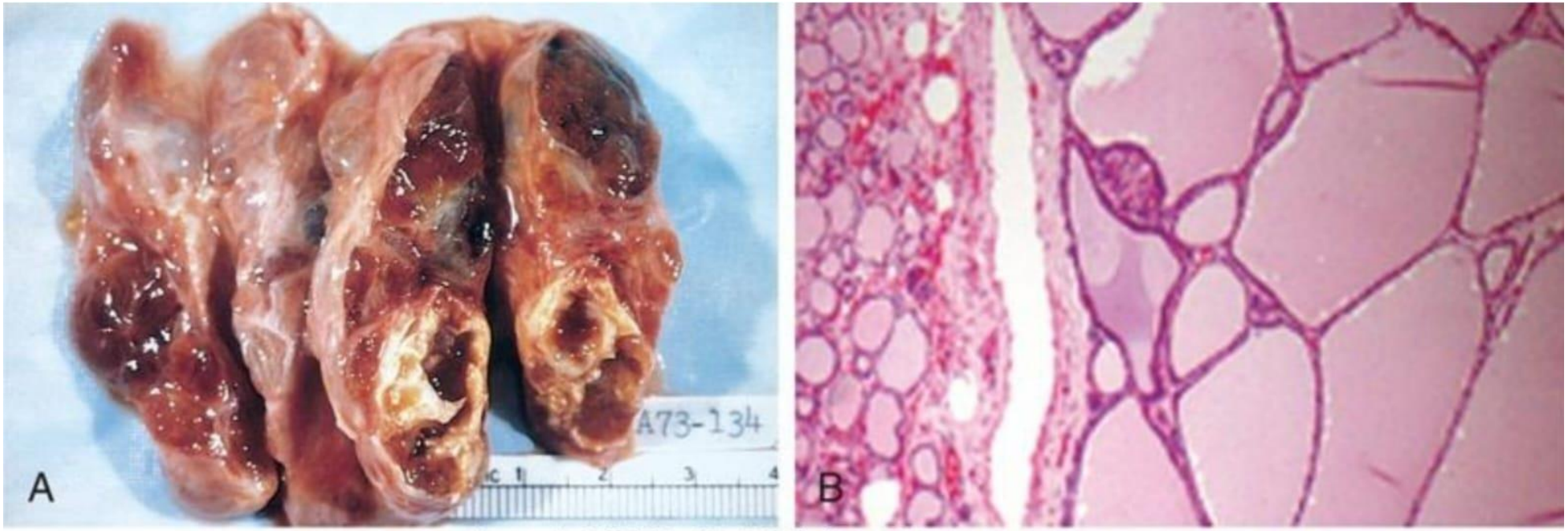
c. With time, recurrent episodes of hyperplasia and involution produce a more irregular enlargement of thee thyroid, termed multinodular goiter and virtually all long-standing diffuse goiters convert into multinodular goiters.

mechanism


No inhibition
Hypothalamus
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



Kumar et al: Robbins Basic Pathology, 9e.
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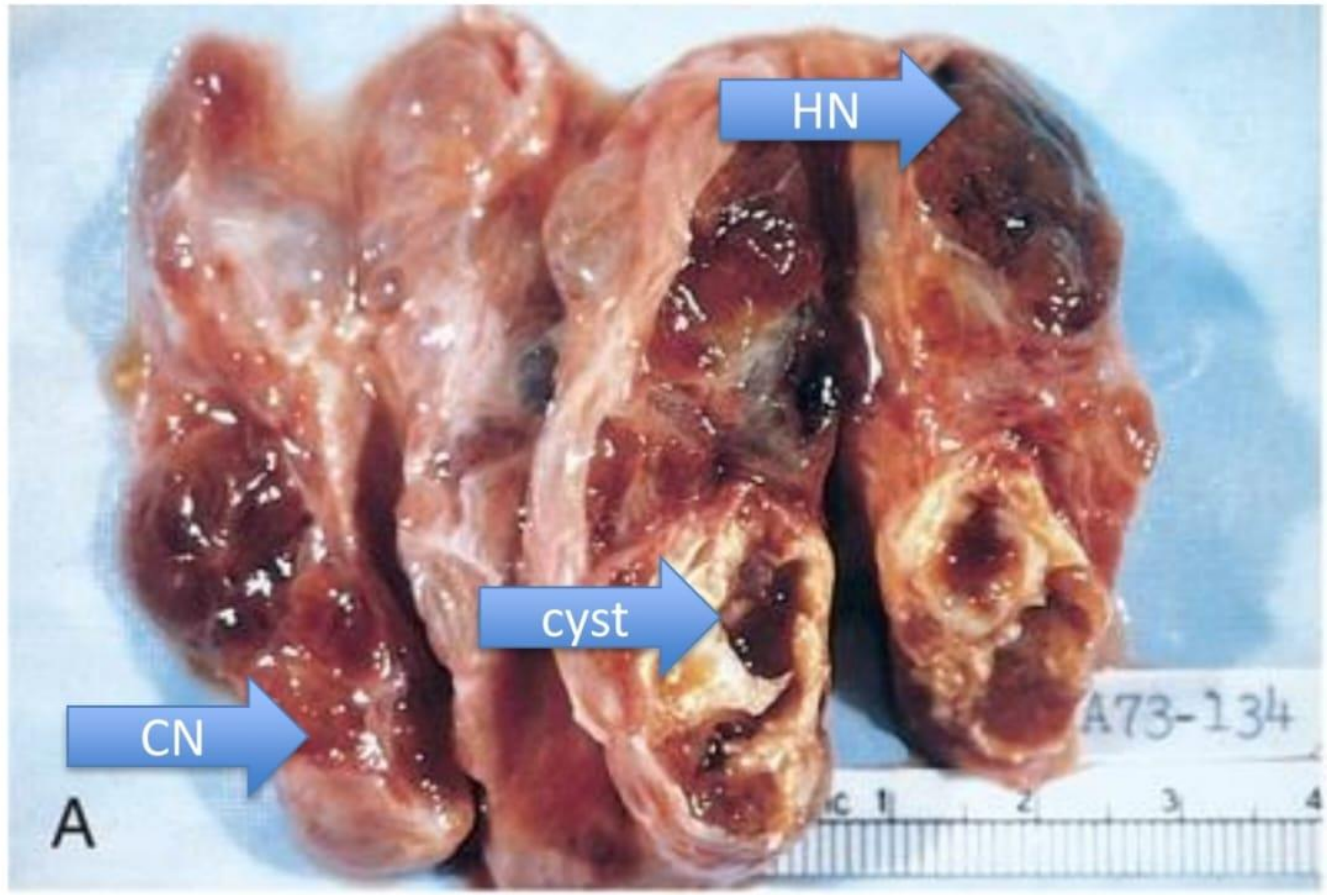
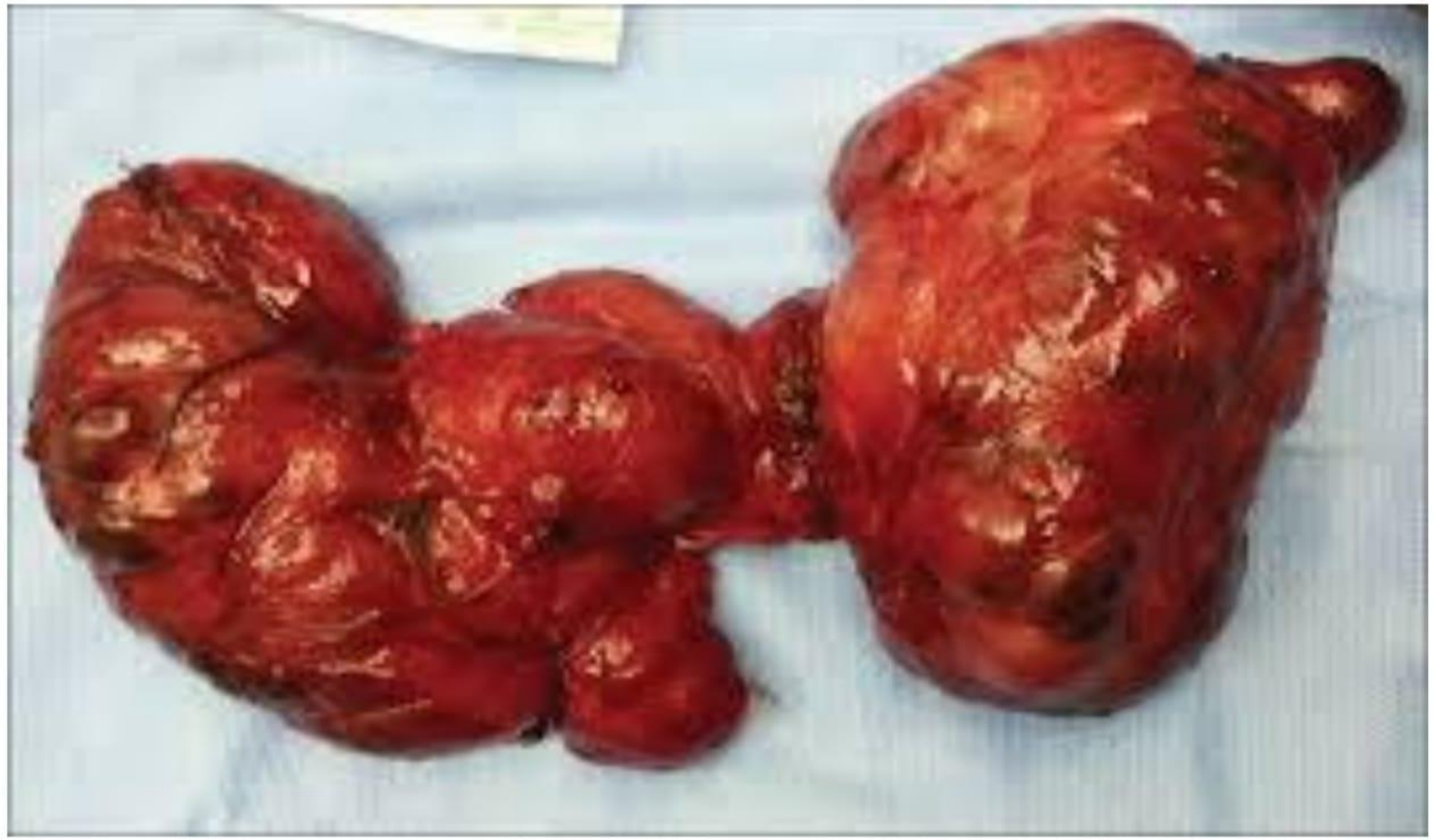
Multinodular goiter: thyroid shows several nodules, some are hemorrhagic (HN), others contain colloid (CN) and some become cystic.



multinodular goiter



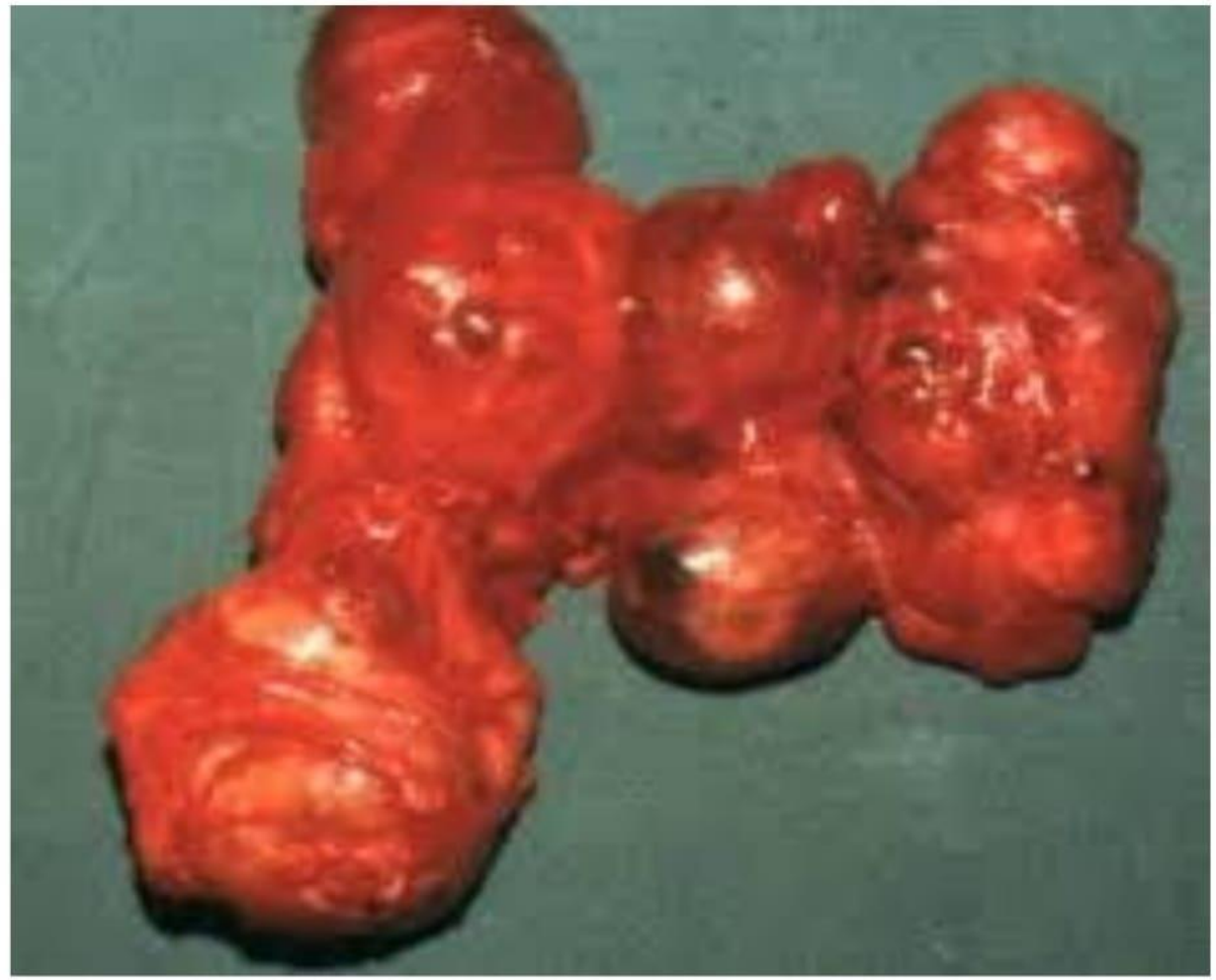
Note:

- 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**

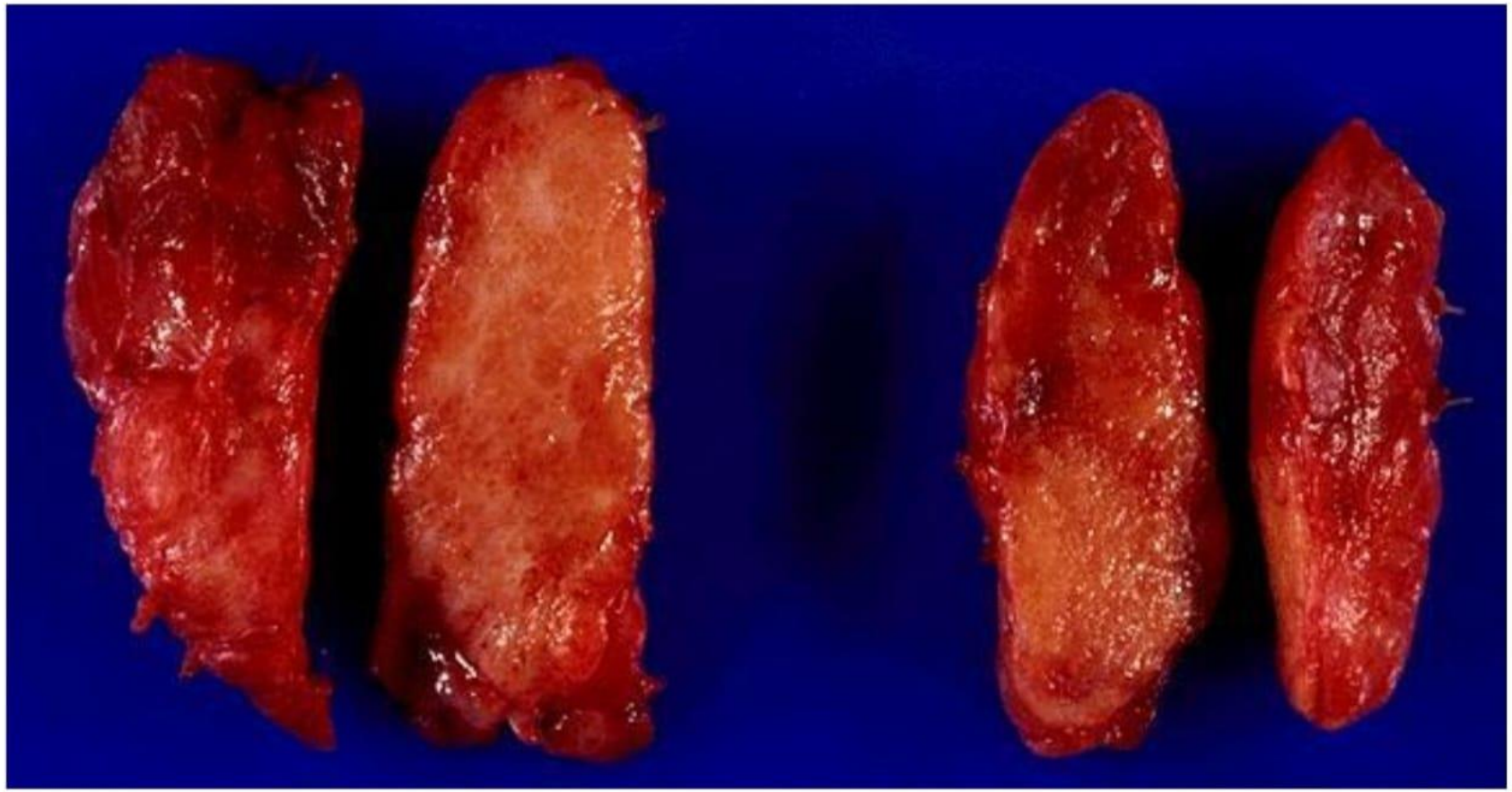
Plummer syndrome: is multinodular goiter which cause one of the nodules to become secratory (secretes T3 & T4) -----> Hyperthyroidism

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

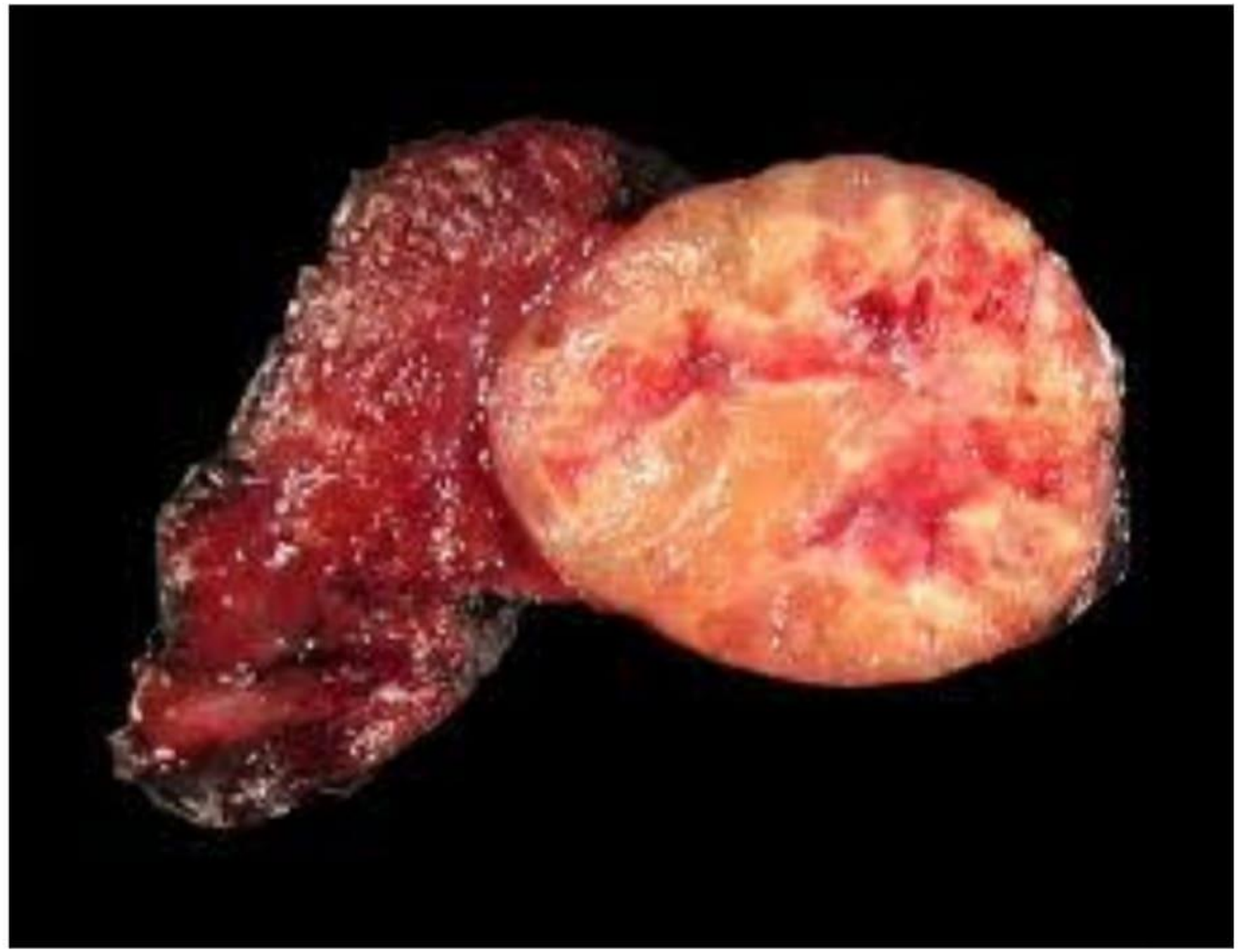
- Case A



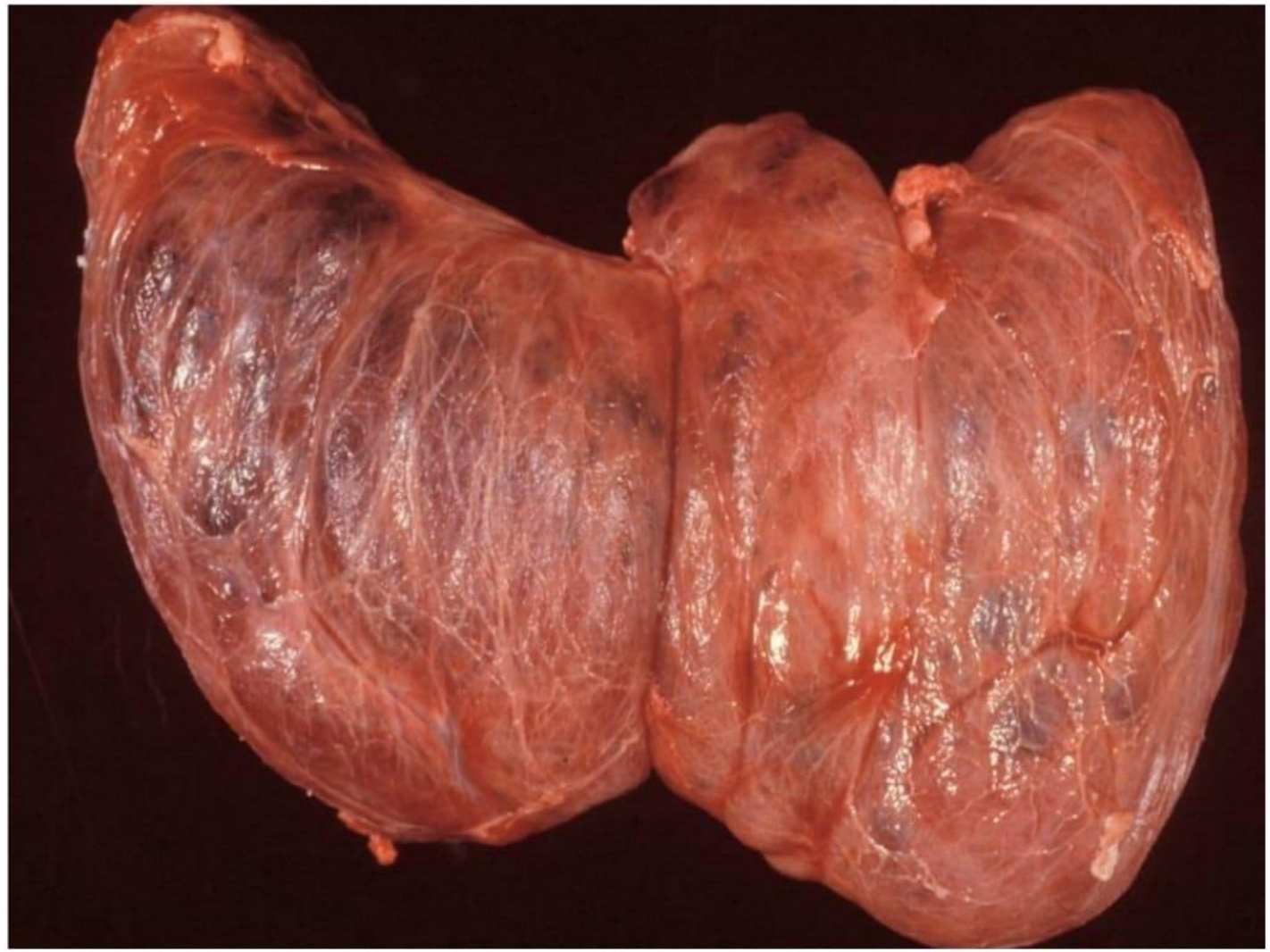
Case B



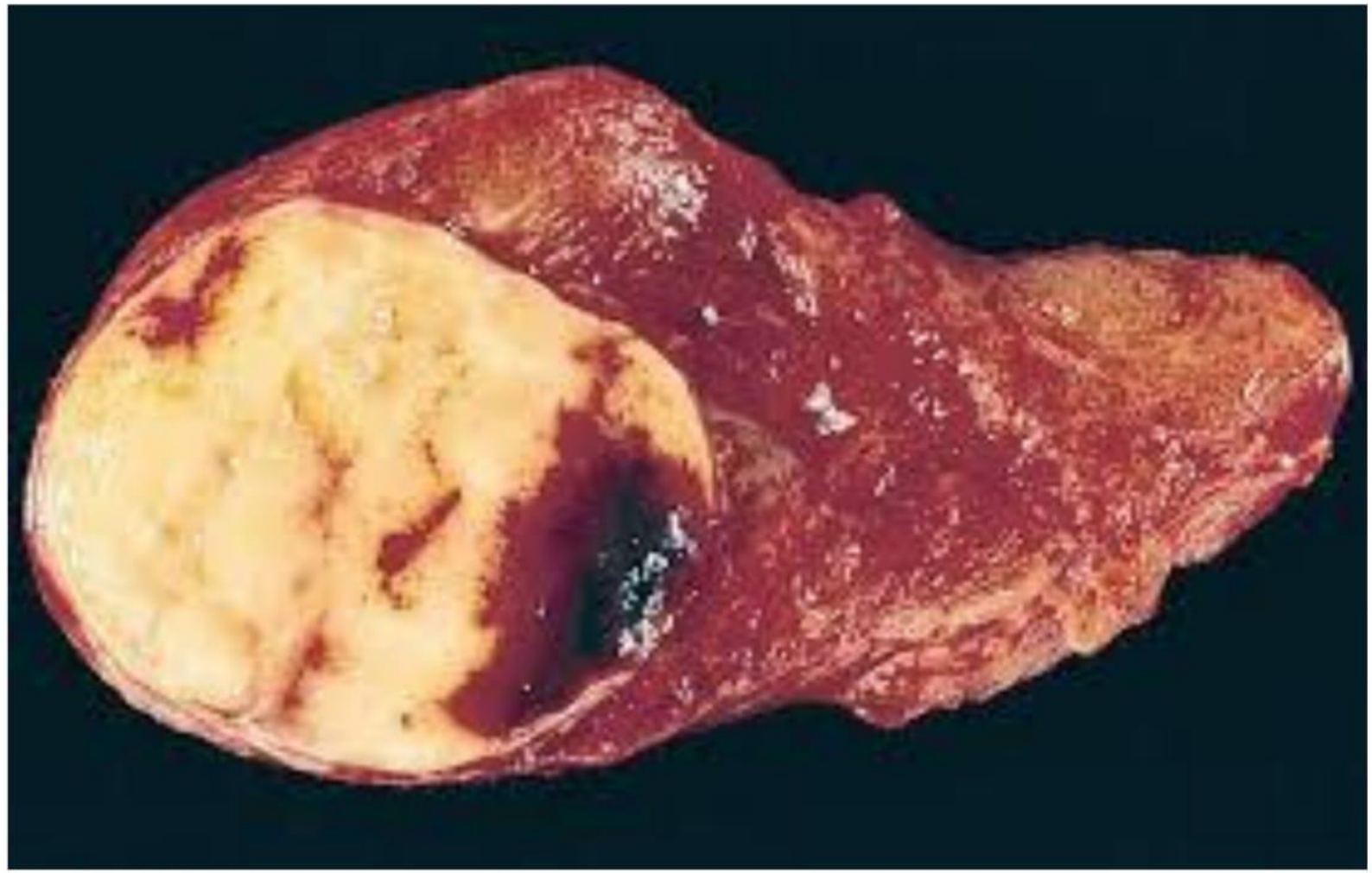
Case C



Case D



Case E

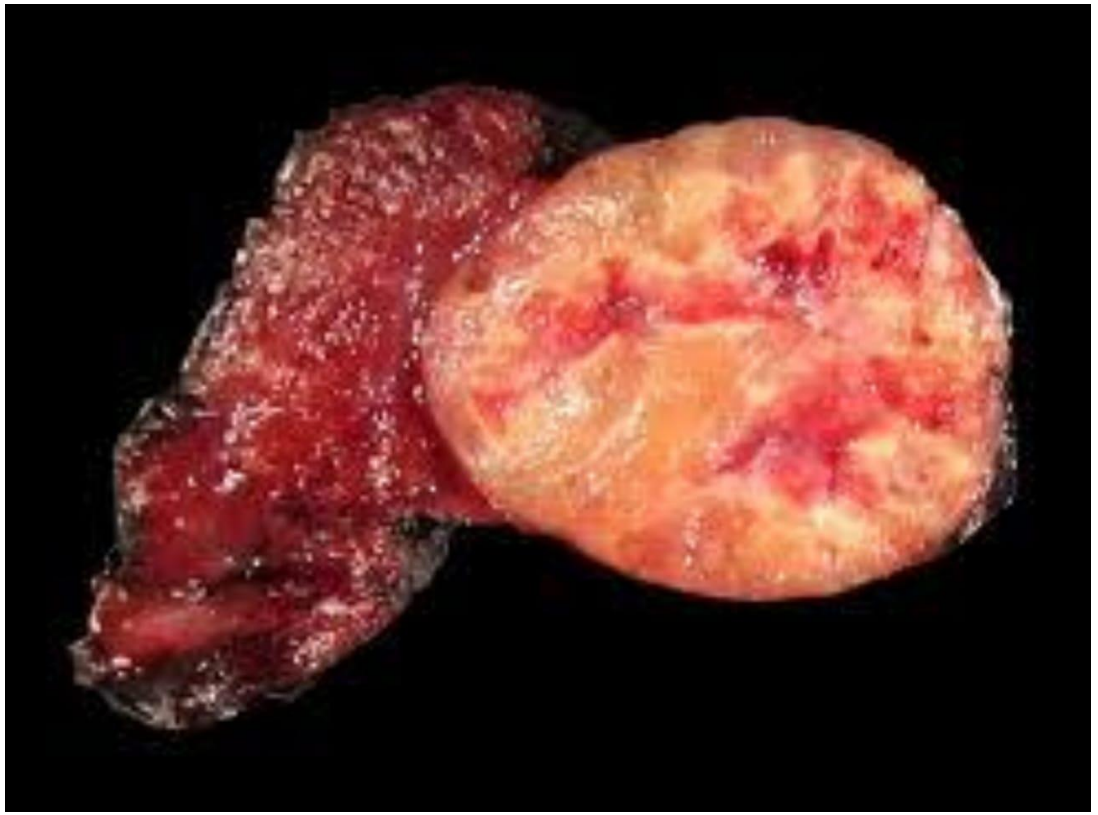


Answers

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

Thyroid tumors

- Thyroid neoplasms present as single nodules
  but not every single nodule is a tumor



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, one type and its variants (example: Hurthle cell adenoma, atypical adenoma).

Malignant (multiple types) :

1. papillary carcinoma.
2. Follicular carcinoma.
3. medullary carcinoma.
4. Anaplatic carcinoma.

Follicular adenomas

- Are benign neoplasms derived from follicular epithelium.
- Solitary.
- The tumor is demarcated and compressed the adjacent thyroid parenchyma by a well-defined, **intact** capsule.
- Usually are cold nodules (non-functioning, do not secrete T3/T4) on scanning *but might be functional (secretory)*.
- Behavior of thyroid adenomas :

a. Carry an excellent prognosis

b. do not recur or metastasize

c. and are *not* forerunners to carcinomas

Microscopic examination of follicular adenoma:

- The cells are arranged in follicles and its **variants**

a. **Hurthle cell** adenoma:

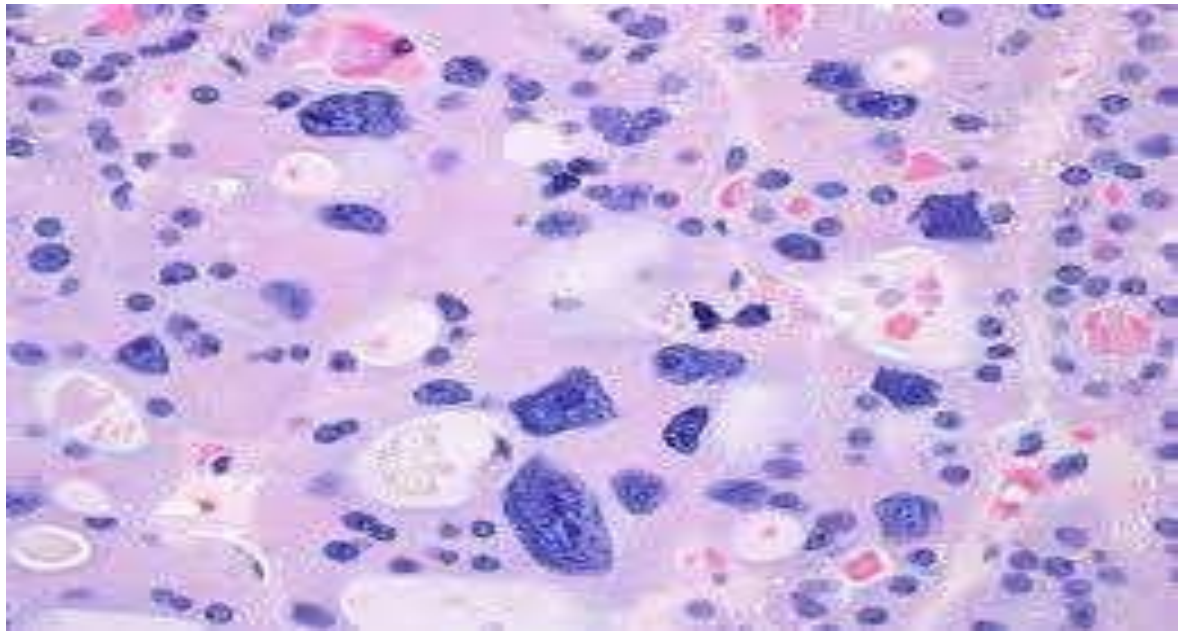
- The neoplastic cells show lining of oxyphil or Hürthle cell change, and its behavior is not different from those of a conventional adenoma.

b. **Atypical** adenoma (no special behavior):

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

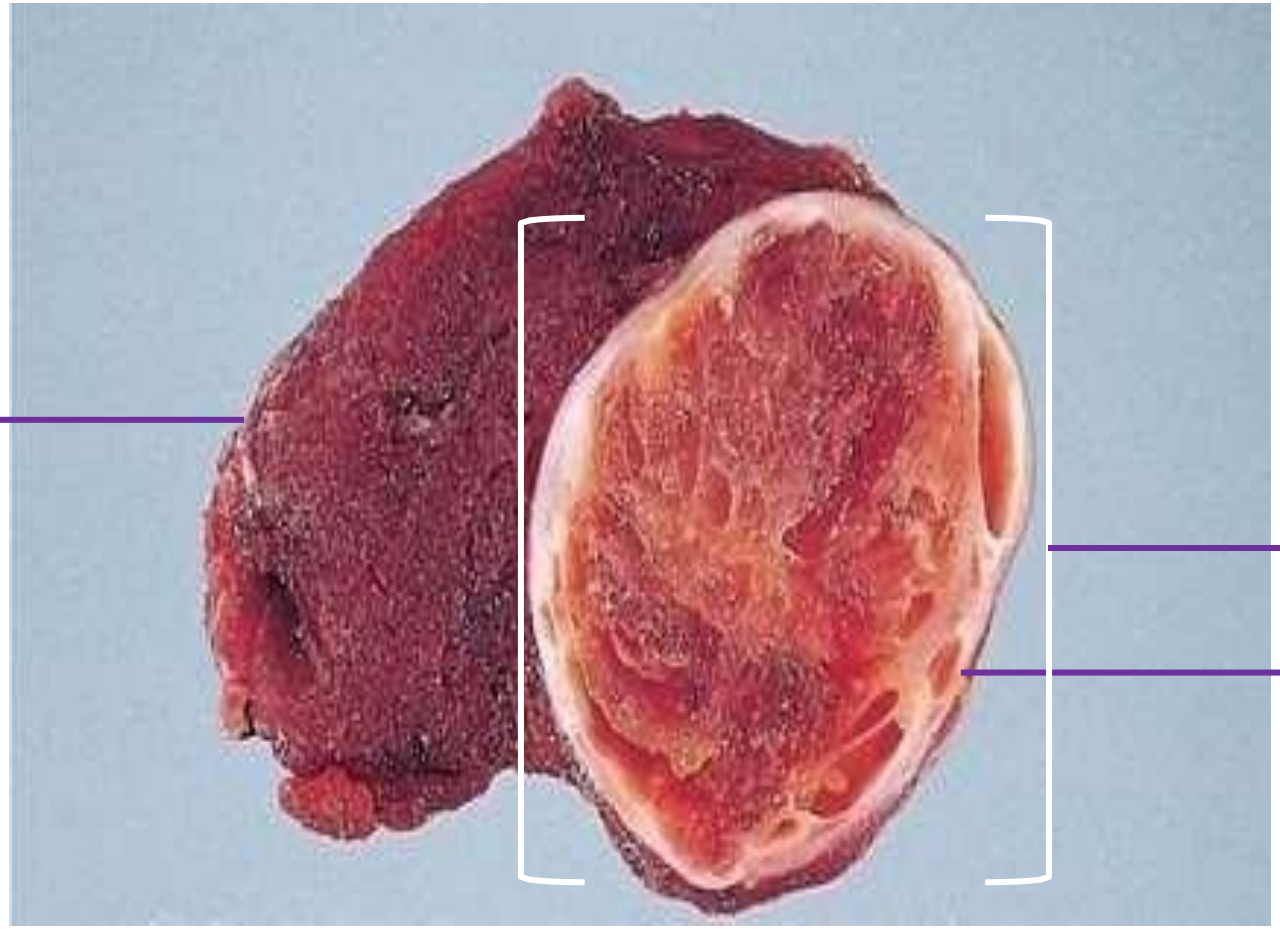
Endocrine atypia

- Note the large, hyperchromatic, pleomorphic cells. These are atypical and this atypia in endocrine glands doesn't necessarily mean malignancy.
- They are like any other follicular adenoma, benign lesion that doesn't metastasize, and neither reoccurs after removal nor is premalignant.



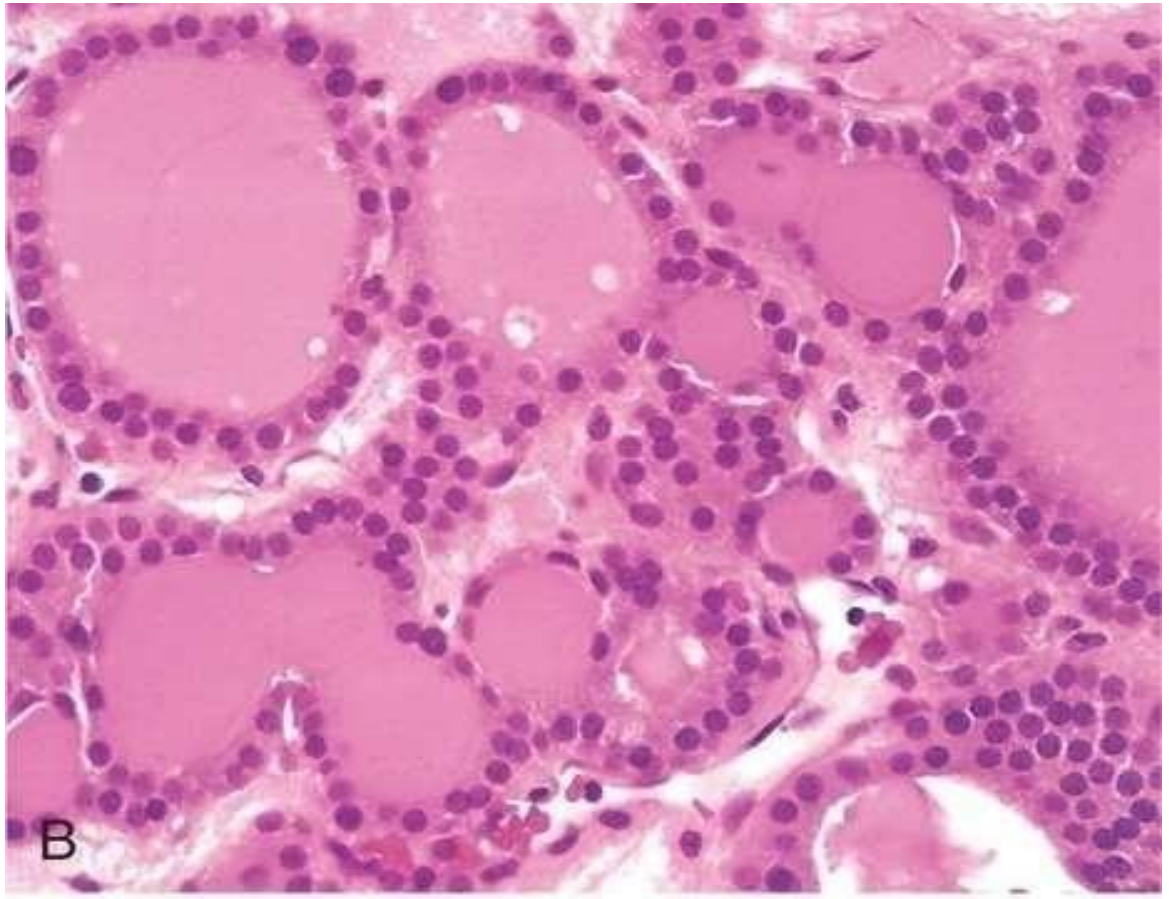
Follicular adenoma

- Well demarcated, encapsulated nodules.



On microscopic examination:

Micro: composed of follicles similar to the normal thyroid follicles (Adenoma can be distinguished only by the surrounding capsule).



Hurthle cell adenoma

- Cells are large with abundant eosinophilic cytoplasm.
- Behavior is similar to that in atypical adenoma.

- 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** (not all cases) of thyroid carcinomas associated with previous exposure to ionizing radiation (has increased after Hiroshima and Nagasaki attacks).
- May occur **at any age**
- **Gross:** Either solitary or **multifocal lesions**

multifocal lesions is exeption

- Note: papillary carcinoma can be multifocal

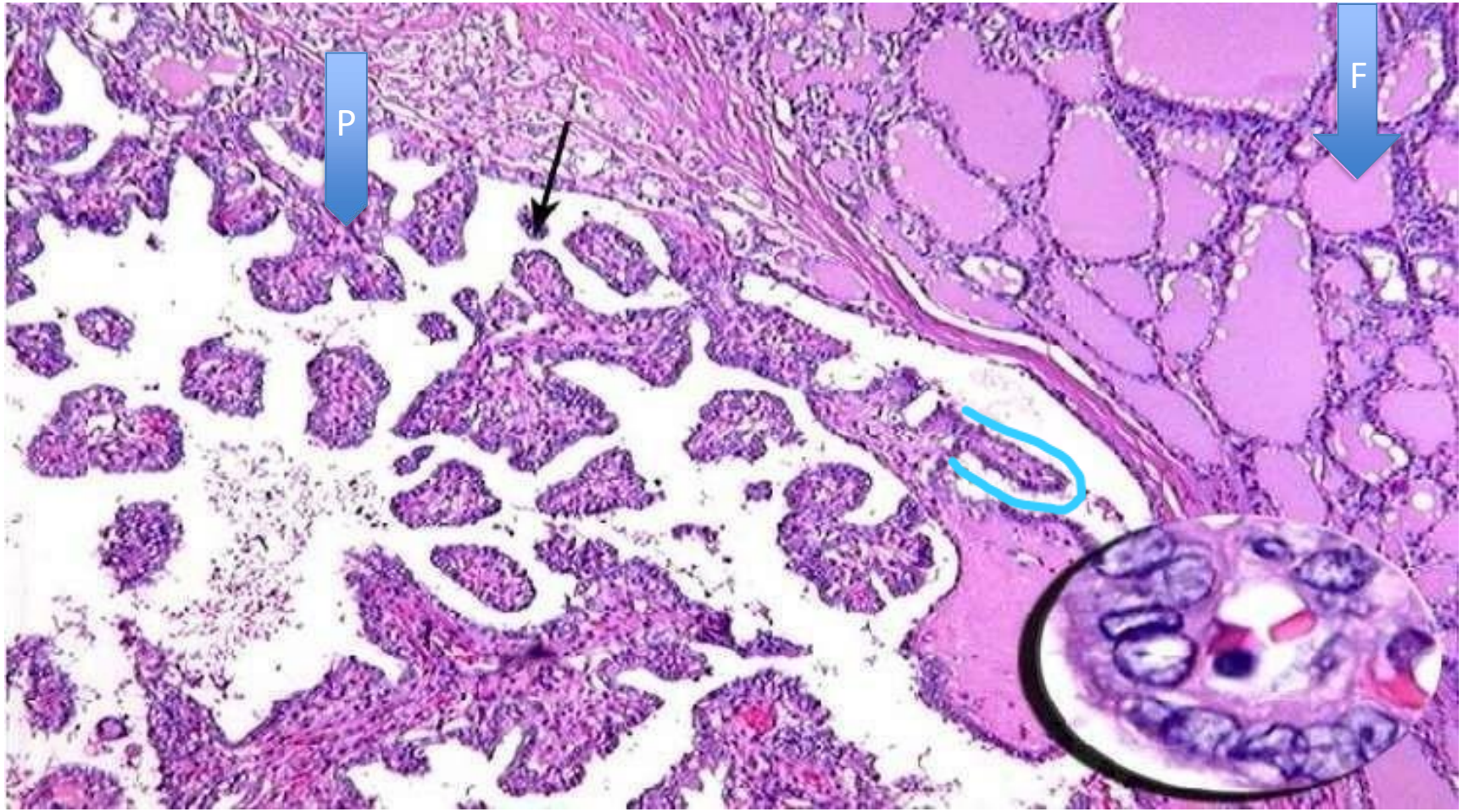
Microscopic features of papillary carcinoma

1. The presence of papillae

2. Nuclear features.
3. Concentrically calcified structures (psammoma bodies).

1. Papillae (P) : finger-like projection.

Note the difference from the normal follicles (F).

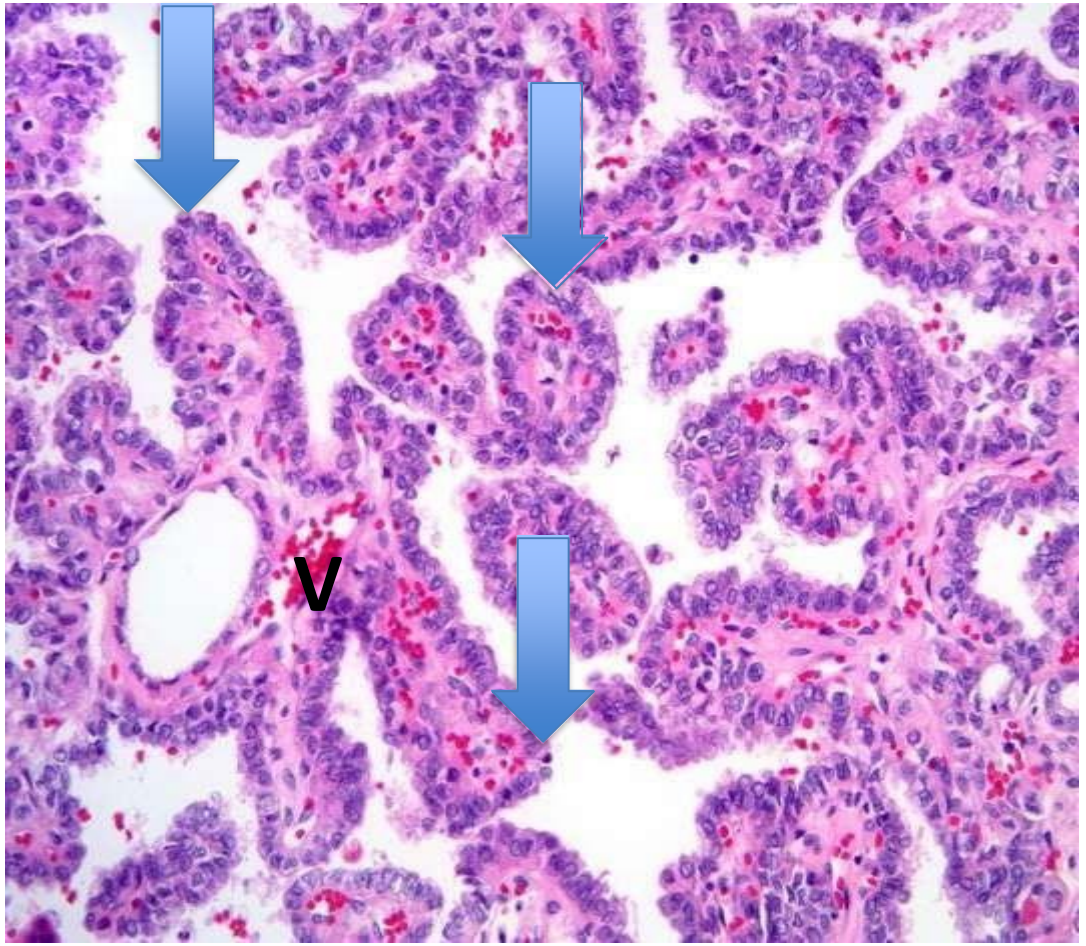


1. Papillae – con.

-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.

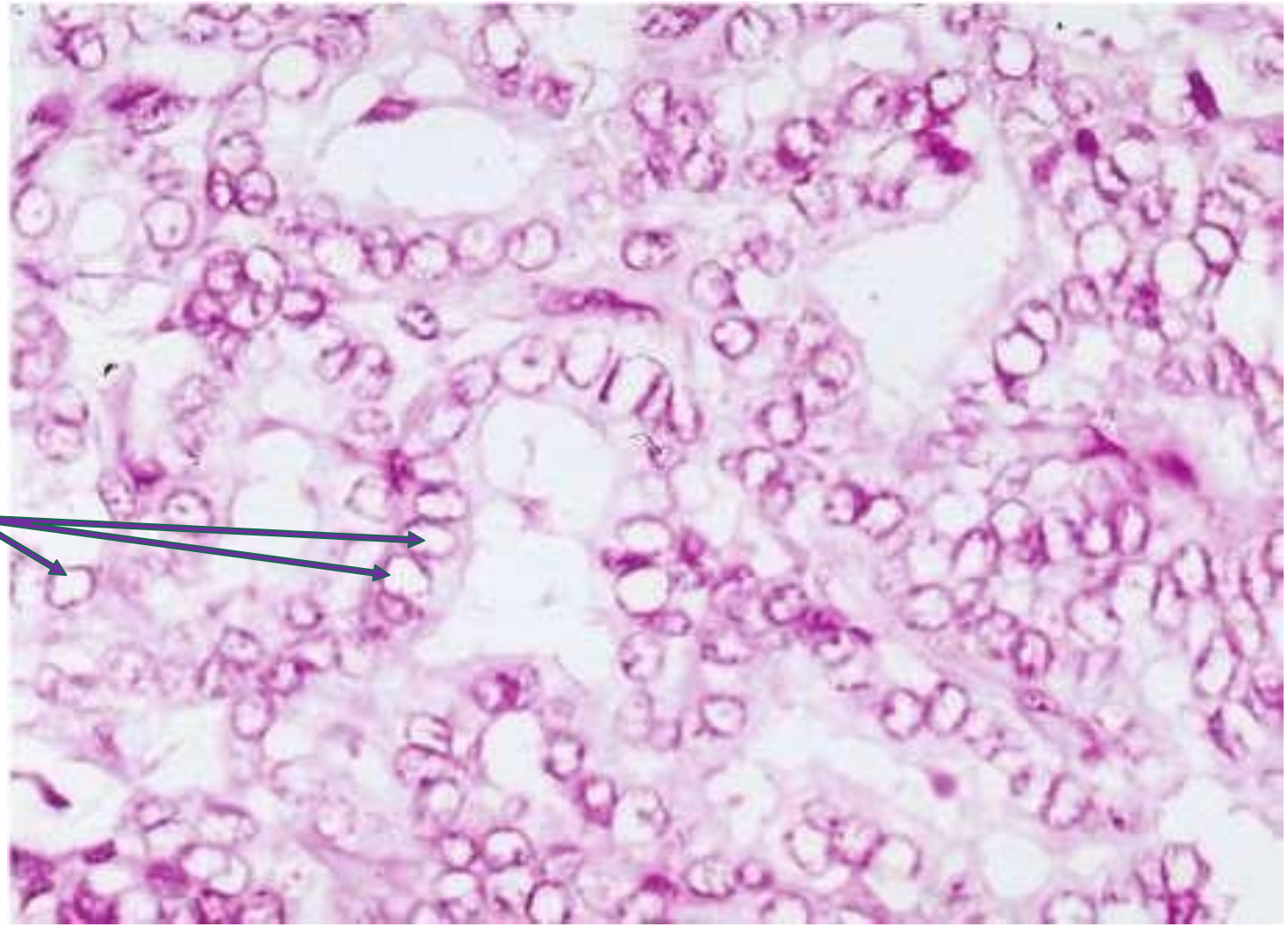


2. Nuclear features of papillary carcinoma

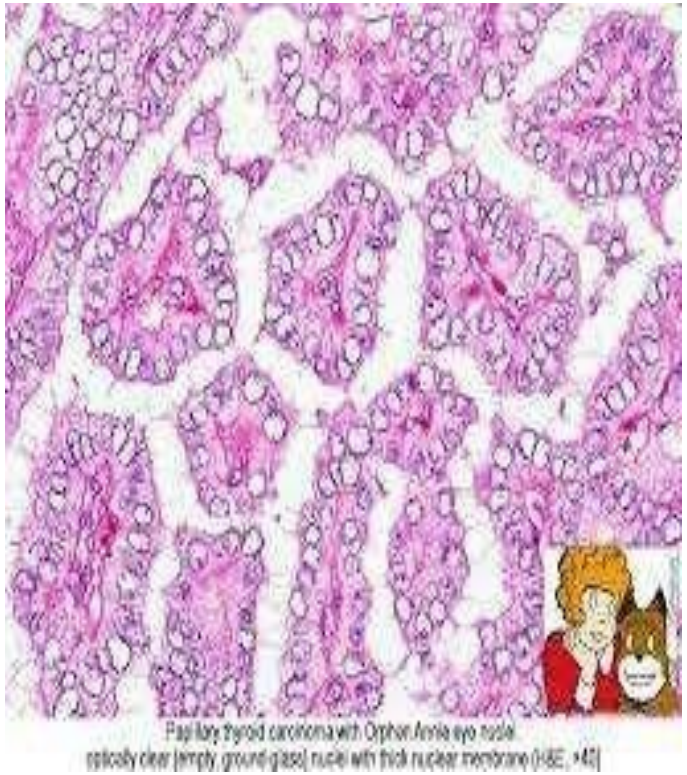
a. Optically clear nuclei, or "Orphan Annie eye" nuclei, seen on histological but not cytological preparations (formalin artefact).
b. Grooves within nuclei: so, the nucleus looks like a coffee bean.
c. Have invaginations of the cytoplasm to the nucleus (pseudoinclusions).

a. Clear nuclei: note the nuclei are white.

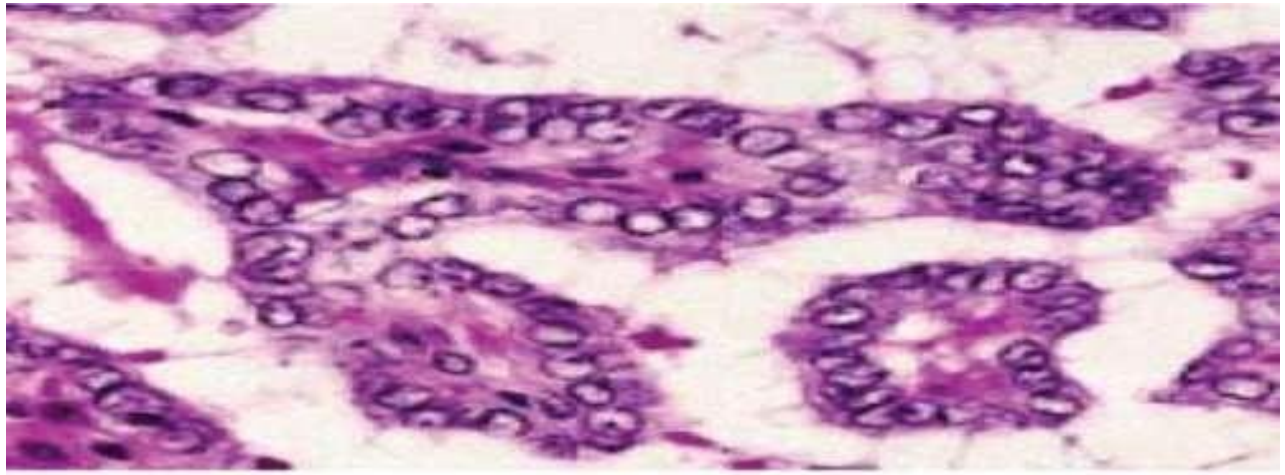
It looks empty internally .



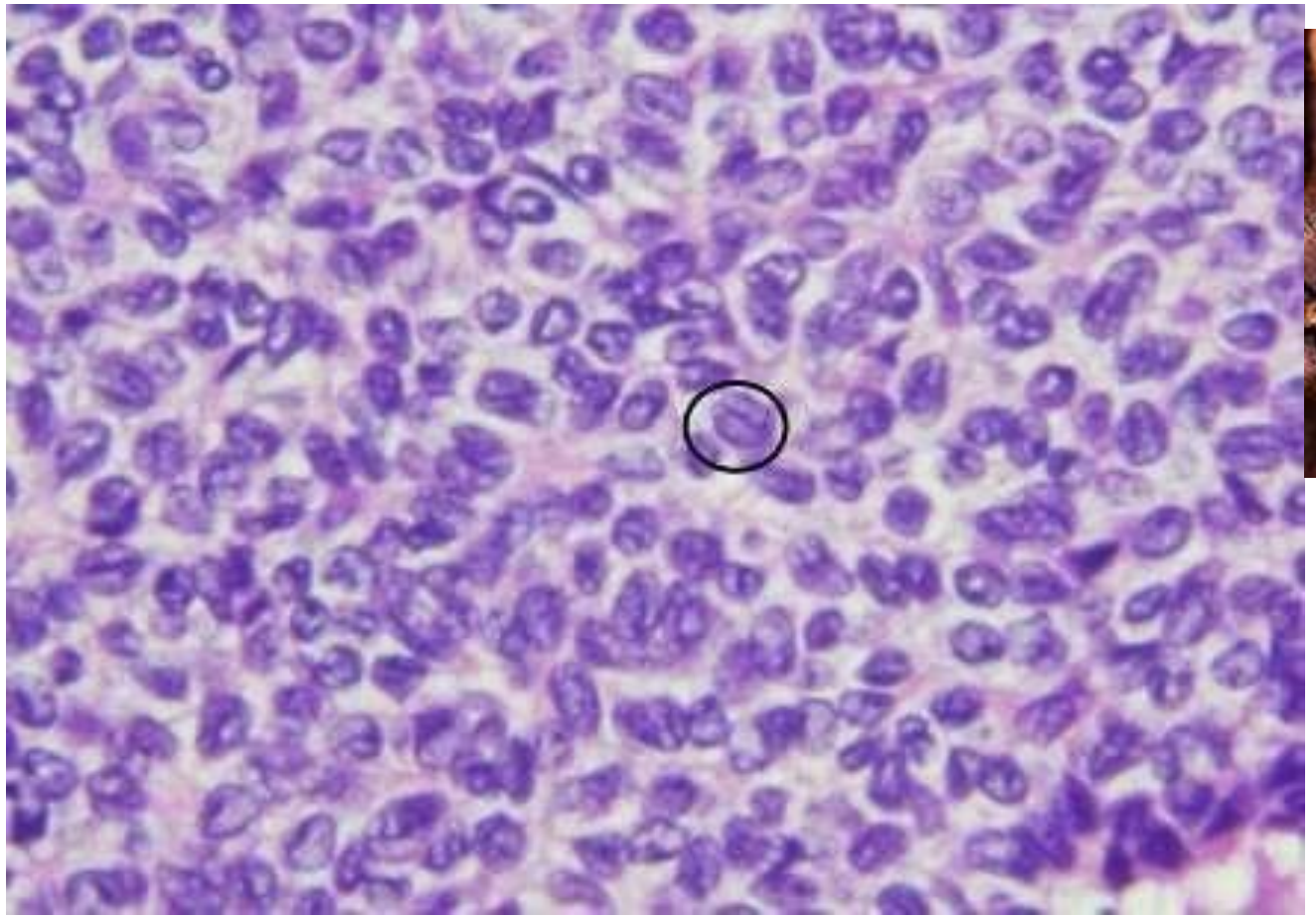
Orphan Annie eye! Because the nuclei are white and empty like Annie's character eyes!!



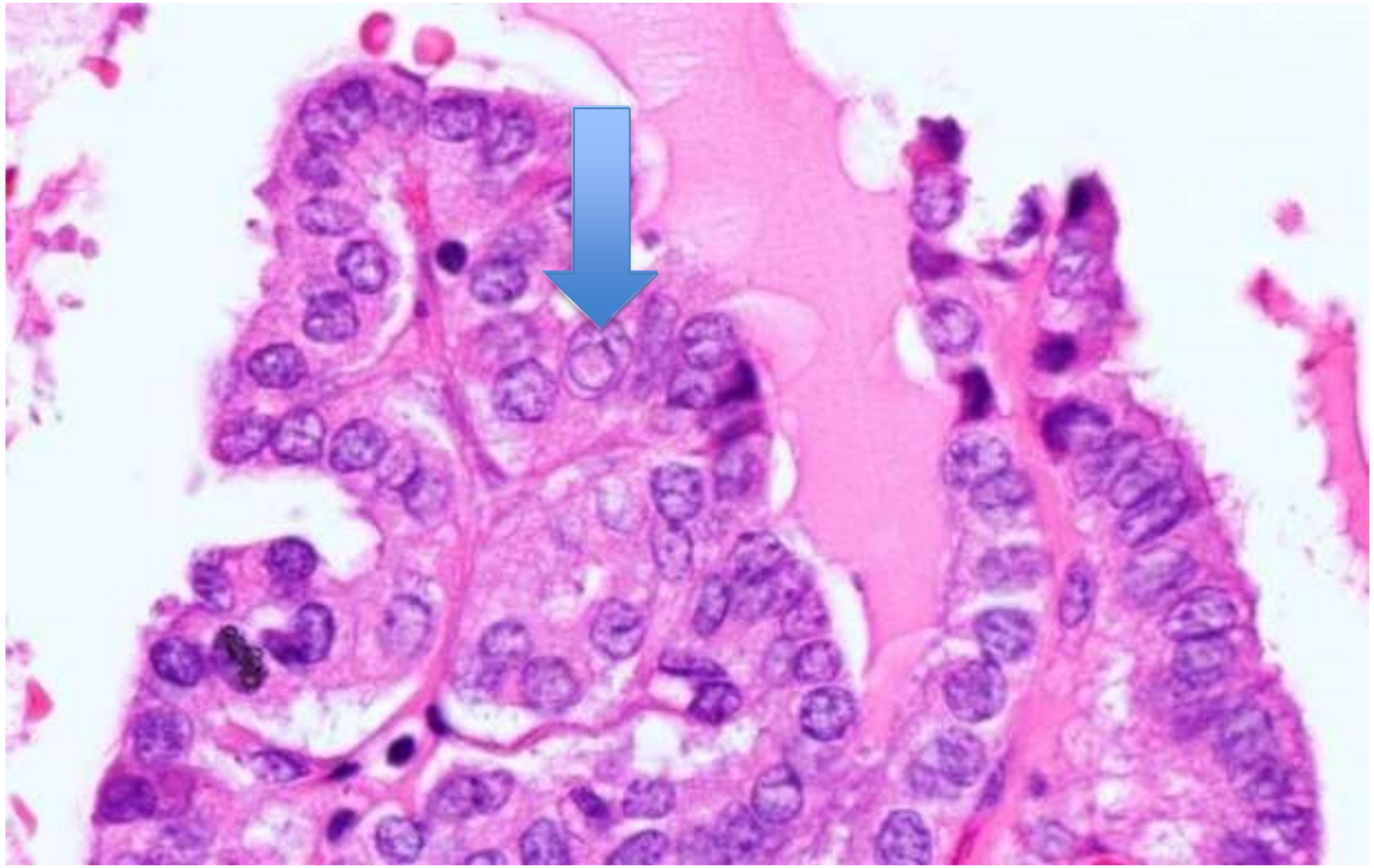
I know what you're thinking: pathological terms are funny.. You’re right



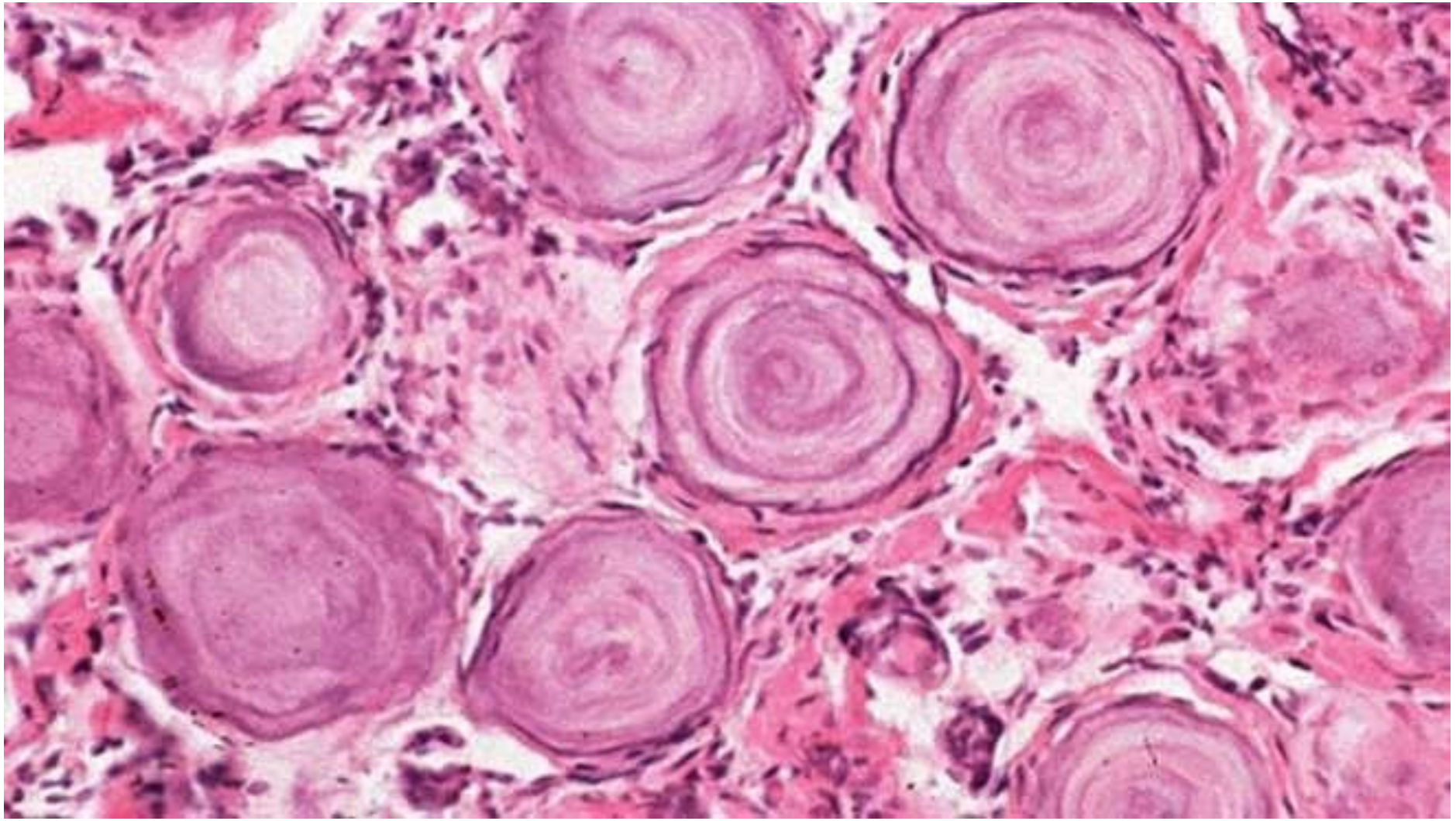
b. Some express nuclear grooves = coffee bean nuclei



c. Nuclear inclusions: cytoplasmic invagination into nucleus, Appear as two nuclei inside one another



3. Psammoma bodies: Concentric calcifications, appear as onions



Papillary carcinoma

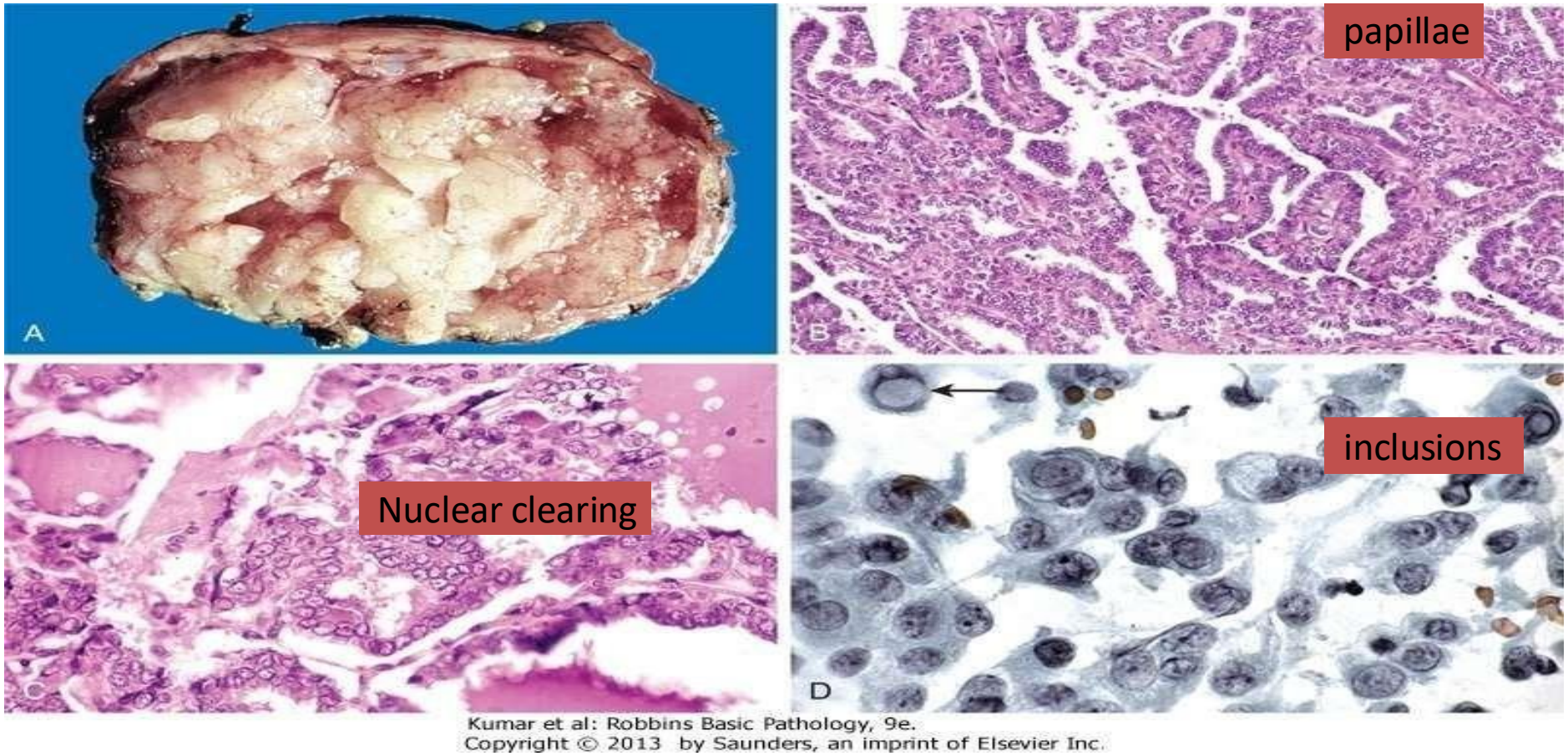


FIG. 18.12 Papillary thyroid carcinoma. (A to C) A papillary carcinoma with grossly discernible papillary structures. In this particular example, well-formed papillae (B) are lined by cells with characteristic empty-appearing nuclei (C), sometimes called Orphan Annie eye nuclei, based on a cartoon character from the 1920s. (D) Cells obtained by ne-needle aspiration of a papillary carcinoma. Characteristic intranuclear inclusions are visible in some of the aspirated cells (arrows). (Courtesy of Dr. S. Gokasalan, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

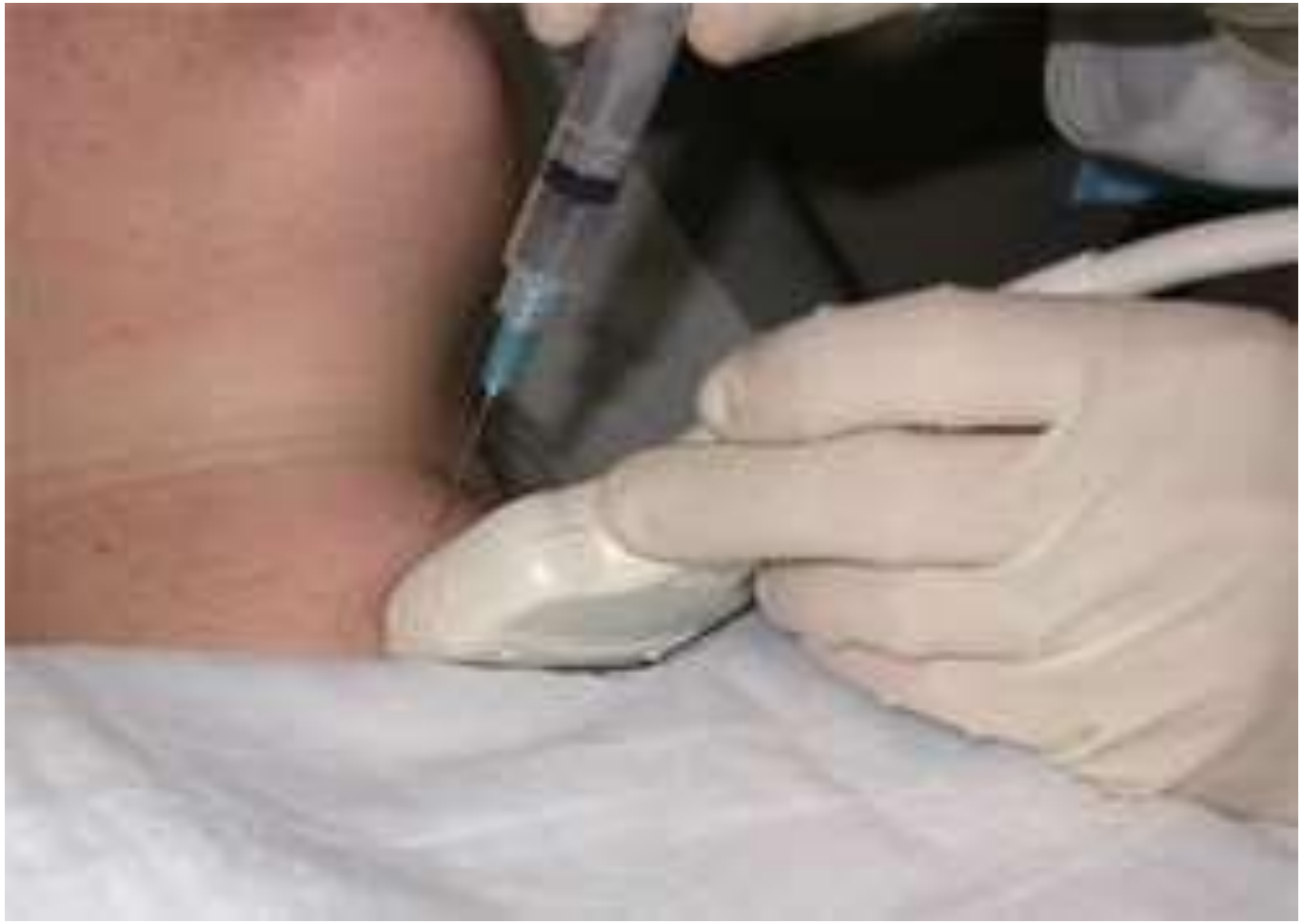
Papillary carcinoma can be diagnosed on FNA

(Fine Needle Aspiration)

Previous histological features are noticed in tissue diagnosis, but a preoperative diagnosis based on the characteristic **nuclear features of cells** can usually be established by fine-needle aspiration.

We start with cells diagnosis, that can be done by cell aspiration via FNA.

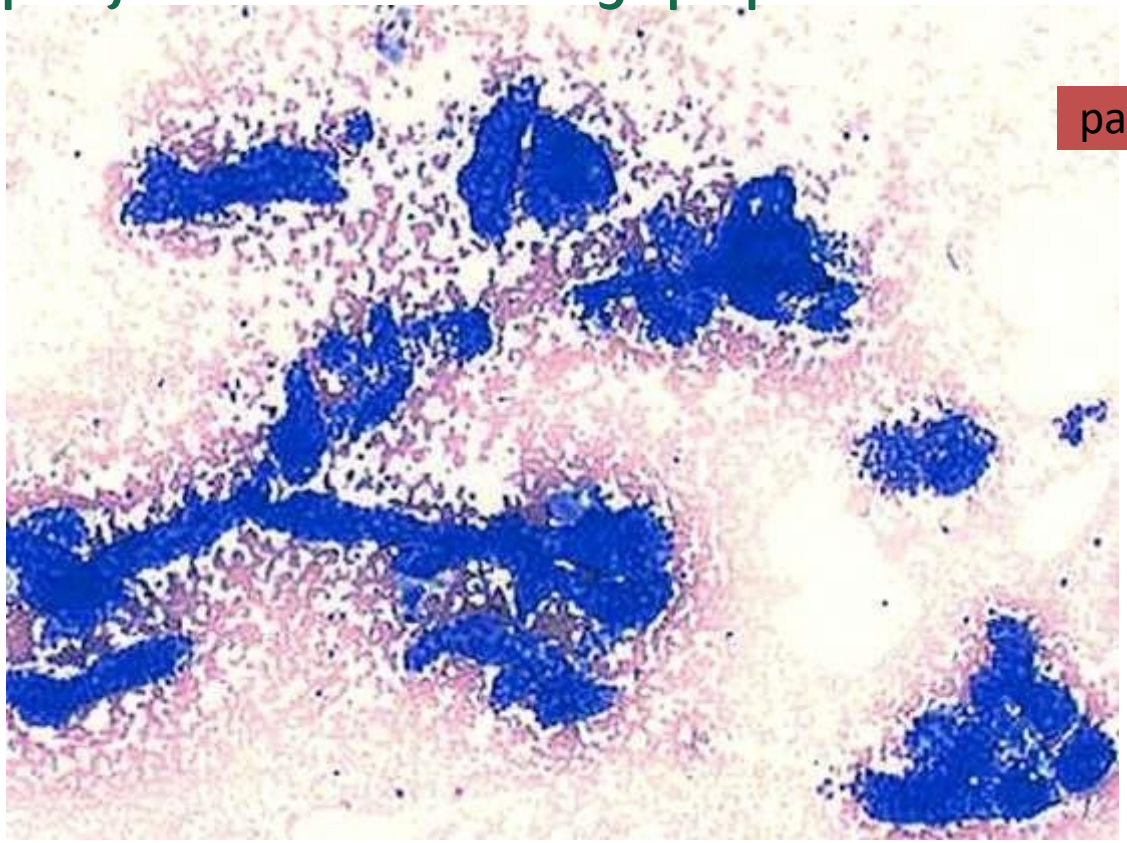
This procedure is widely used because it is cheap and with no complications.



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

Even if we took FNA, the structure still shows the papillae due to the connection between cells which preserve the structure allowing to establish diagnose.

These are not follicles, but finger like projections forming papillae

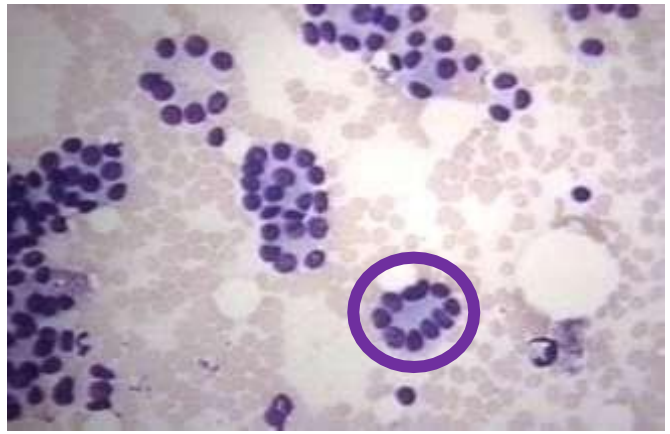


papillae

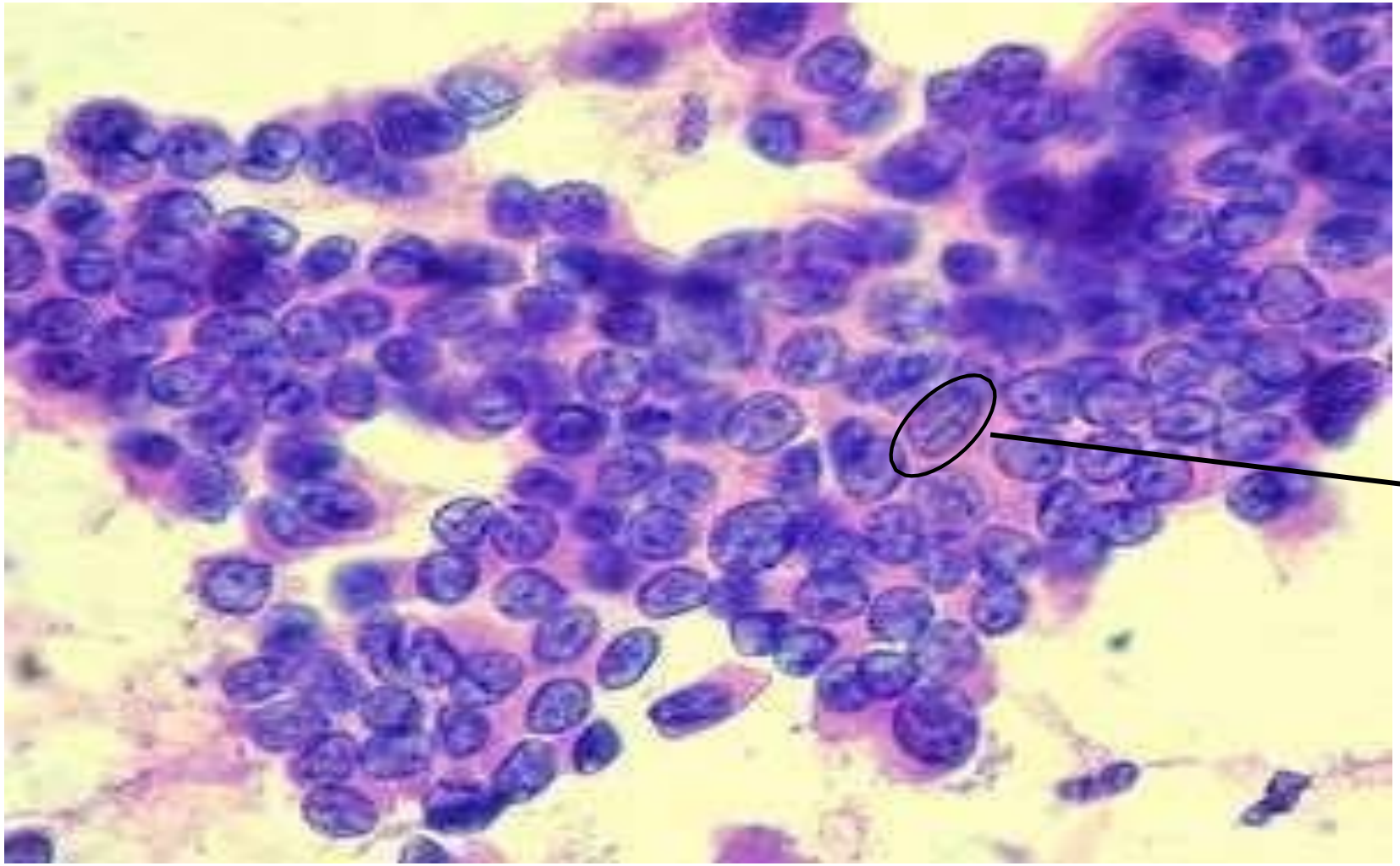
But they do not always form papillae,so the pathologist should search for the nuclear features discussed earlier

Normal cells

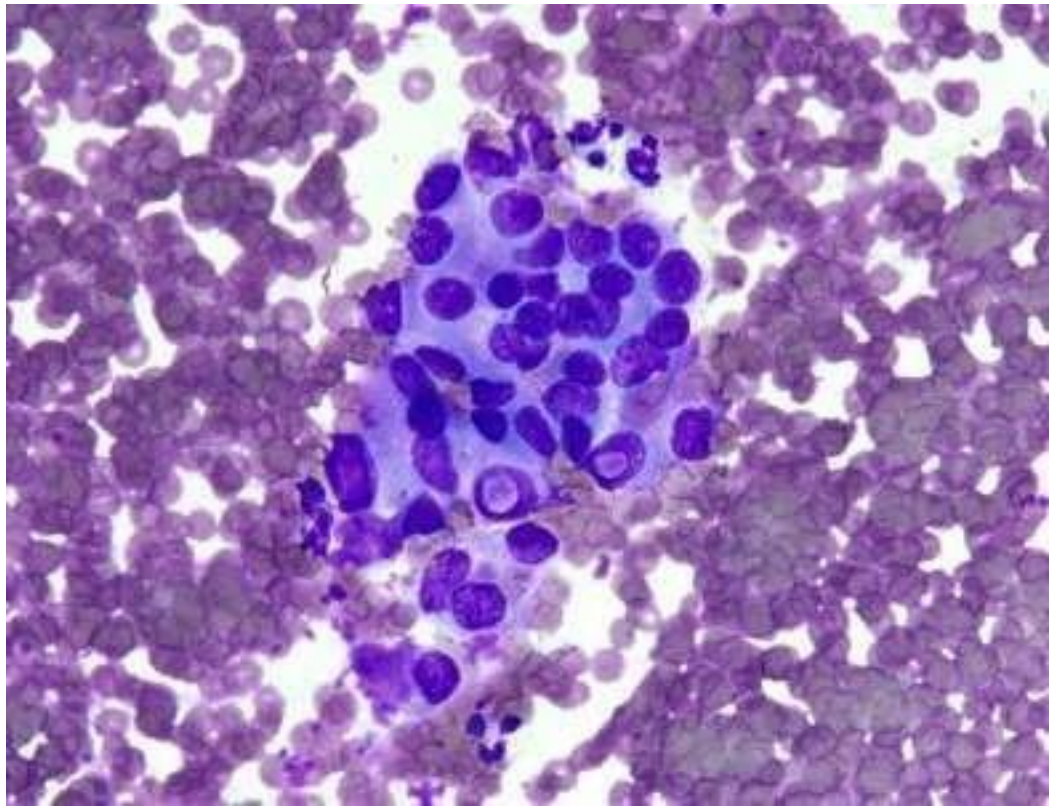
follicles

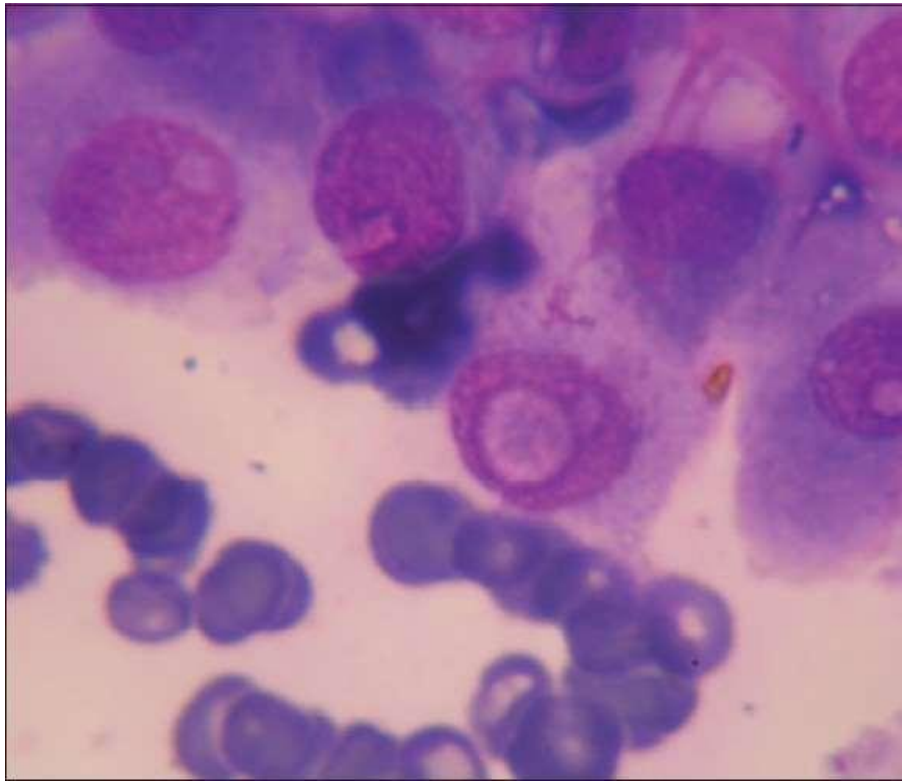


Grooves seen on FNA

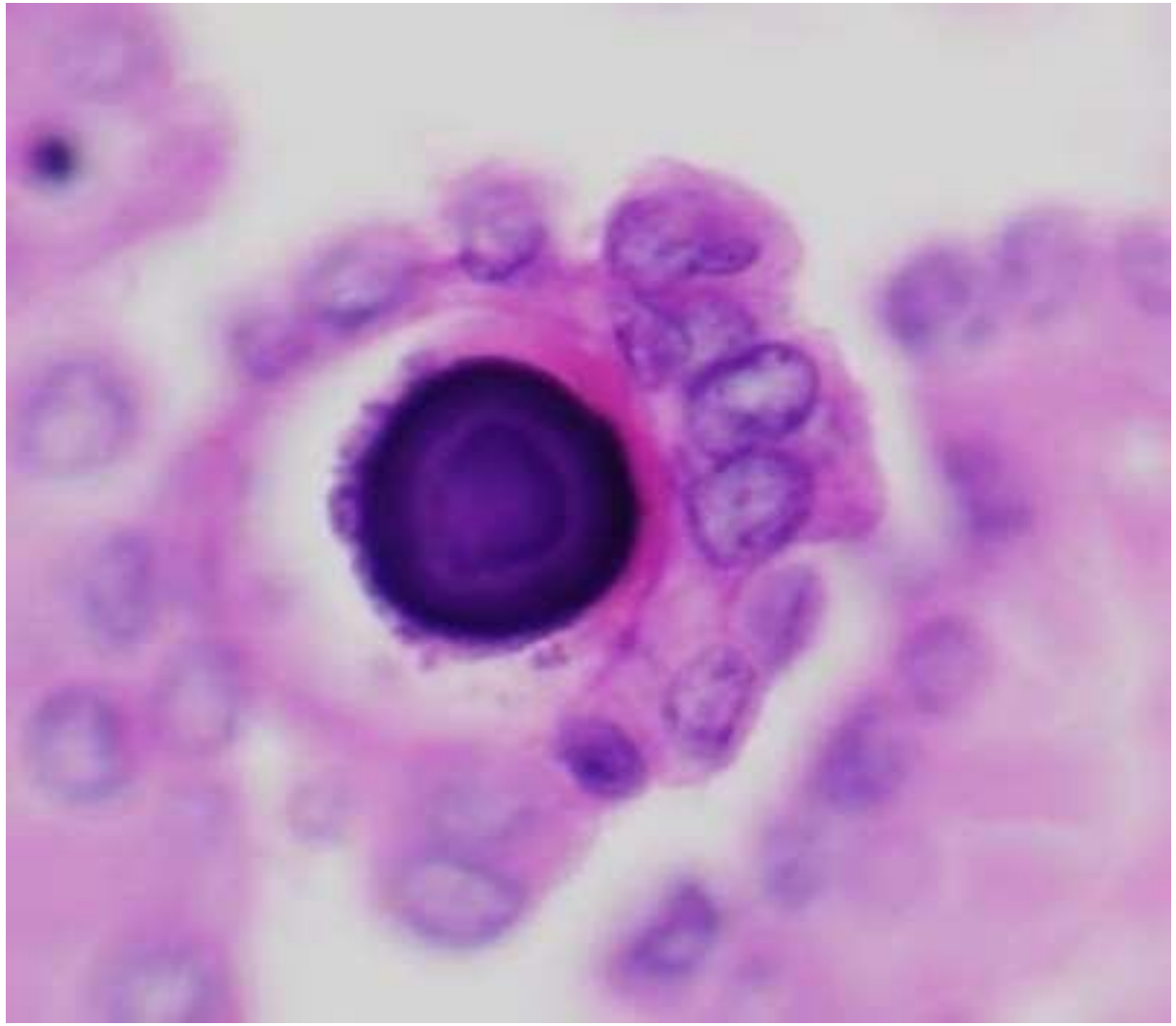


Inclusions seen on FNA





Psammoma bodies can be seen on GNA (Giemsa-stained fine needle aspirate smears)



Notes

- Clear nuclei are not seen in FNA because they are an artefact due to formalin.
- Formalin is used to fix *tissues* before staining them with H and E
- In cytological (FNA) preparations we use alcohol as a fixative, no formalin is used. So, no clearing artefact.
- Formalin causes an artefact (only in papillary carcinomas) which causes the nucleus clearing.

- The summary: Every microscopic feature in histological sections of Papillary Carcinoma is seen in FNA except the Orphan Annie eye nuclei.

Frozen section

In a frozen section, the nuclear chromatin remain distinctly visible , resulting in loss of chromatin clearing as a characteristic nuclear feature .
The patient may be undergoing surgery, and the pathologist needs to examine the tissue intraoperatively to help determine the diagnosis and guide surgical management .
The tissue is rapidly frozen and examined within approximately 20 minutes. In this technique, the tissue is frozen rather than fixed in formalin. Formalin is not used before freezing, because the tissue needs to be frozen directly using ice/freezing material .

Clinical Features of papillary carcinomas

a. Are nonfunctional tumors 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% and 5-year survival rates of 99%, indicating excellent prognosis.

c. The presence of isolated cervical nodal metastases does not have influence on good prognosis of these lesions Even if the tumor metastasizes to a single lymph node, the prognosis is still good.

d..(28:30)

e. In a minority (very rare) of patients, hematogenous metastases are present at the time of diagnosis, most commonly to lung.

Lymphatic spread and Metastasis

Papillary carcinoma commonly spreads through the lymphatic system, The spread of papillary carcinoma starts with involvement of the lymph nodes and later or at a very late stage...the tumor reaches the bloodstream, and once that occur , the prognosis becomes worse because hematogenous dissemination allows the tumor to spread to distant sites .

Genetic factors related to papillary carcinoma

- Mainly 2 genes are involved:

1. BRAF amplification.
2. RET gene rearrangement resulting in a novel protein kinase.

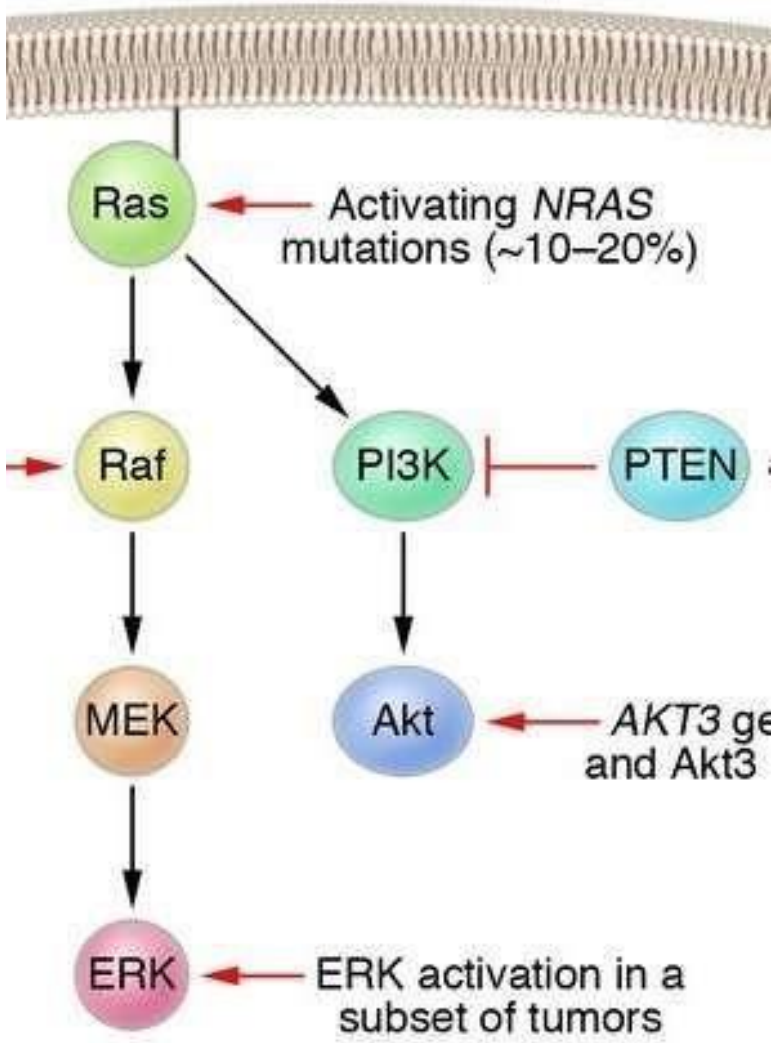
- Remember from the neoplasia lectures that neoplasms occur if there is mutation increasing the effect of an oncogene or decreasing the effect of a tumor suppressor gene. Also DNA repair genes and apoptosis genes can be involved.
- In papillary thyroid carcinoma, 2 oncogenes can be upregulated: BRAF via amplification and RET (tyrosine kinase) via translocation (or rearrangement).

1. BRAF

- Activating point mutations in *BRAF* can be seen in papillary thyroid carcinoma.

- BRAF as an oncogene:

- Remember that **RAS** is the **most commonly mutated oncogene.**
- RAS acts via second messengers, RAF is one of them, BRAF (of the RAF family genes) is an oncogene in the RAS pathway.



2. 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. (recall Philadelphia chromosome)
- RET rearrangement is present in 20% to 40% of papillary thyroid cancers.

RET rearrangement results in the formation of a new kinase activity .
This mechanism is similar in concept to the Philadelphia chromosome, in which chromosomal rearrangement produces an abnormal tyrosine kinase .

RET/PTC

The frequency of *RET* rearrangements is significantly higher in papillary cancers arising after **radiation** exposure.

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

PTC: papillary thyroid carcinoma

Follicular Carcinoma:

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

  thus, The incidence of follicular carcinoma has declined in recent years, coinciding with the introduction of iodine supplementation in table salt
- 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.

b. Minimally invasive that may be impossible to distinguish from follicular adenomas on gross examination and that 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*) (it is considered as an aggressive tumor with poor prognosis)to lungs, bone, and liver.
- Regional nodal metastases are uncommon .
- As many as half of patients with widely invasive carcinomas succumb to their disease within 10 years, while less than 10% of patients with minimally invasive follicular carcinomas die within the same time span.

Follicular Carcinoma

Follicular carcinoma is associated with iodine deficiency & Unlike papillary carcinoma, follicular carcinoma does not have any specific characteristic features as papillary carcinoma. The distinction between a follicular adenoma and follicular carcinoma depends mainly on the presence of capsular and/or vascular invasion and, in some cases, metastasis .

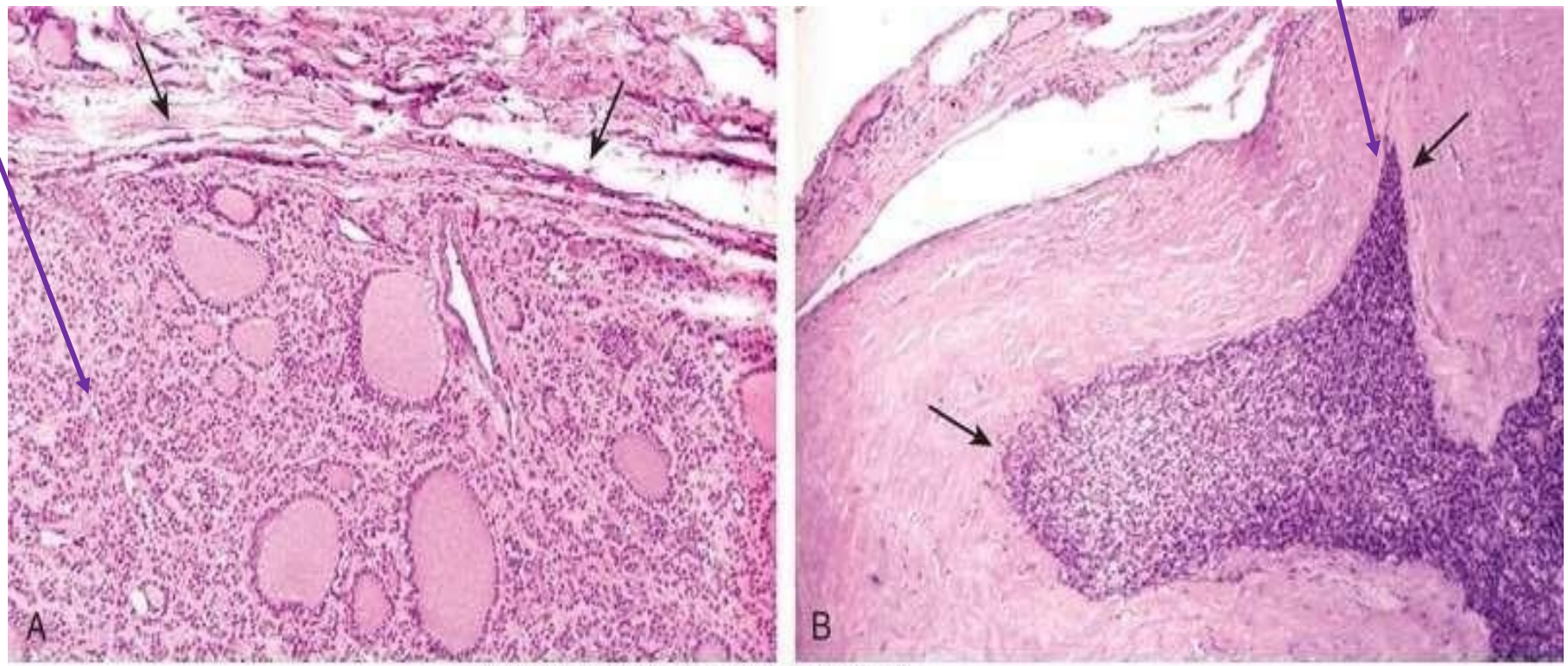
invasion and metastasis are what establish malignancy .

Follicular carcinoma

FNA can't be used for follicular carcinoma diagnosis because these cells can emphasize follicular lesions but can never distinguish whether it is adenoma or carcinoma, so deeper sections are necessary to confirm the presence or absence of capsule invasion, which is known to be a carcinoma hallmark.

- Notice the normal follicle formation with no Atypia

Notice the invasion



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GENETIC FACTORS

Follicular thyroid carcinomas:

a. Gain-of-function point mutations (activation) of *RAS* & *PIK3CA*

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

c. A unique (2;3) translocation presents in one third to one half of follicular carcinomas which creates a fusion gene composed of portions of PAX8, a gene that is important in thyroid development, and the peroxisome proliferator-activated receptor gene (PPARG), whose product is a nuclear receptor implicated in cell differentiation.

At least one question is asked annually about this specific topic.

	Papillary Carcinomas	Follicular Carcinoma
Related conditions	Associated with previous exposure to **ionizing radiation**	**Dietary iodine deficiency**
Behavior (metastasize via) :	Lymph nodes, indolent with good prognosis	Blood (even it is carcinoma) Poor prognosis
Diagnosis	Presence of specific histological and nuclear features.	Only by capsular invasion (NO nuclear features)
FNA utility	Could be used	Can't be used
Mutations	BRAF & RET gens	RAS, PTEN, (2;3) translocation

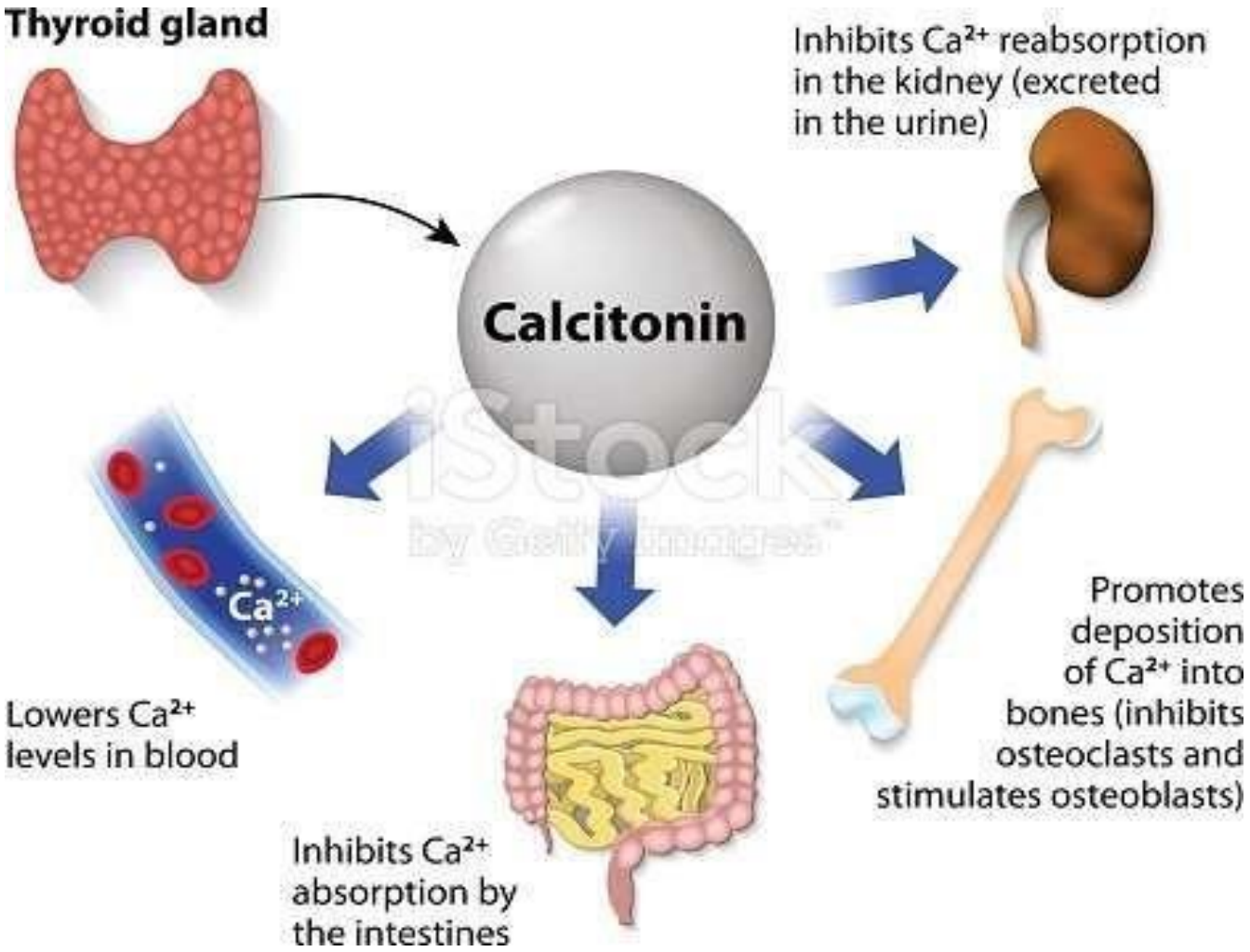
3. Anaplastic Carcinoma

- Rare tumor.
- Are undifferentiated tumors of the thyroid epithelium.
- The mean age of 65 years.
- They are very aggressive, with a mortality rate of 100%, they usually die within the first year.
- 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:** Inactivation of *TP53*, restricted to anaplastic carcinomas and may also relate to their aggressive behavior

4. Medullary Carcinoma

- neuroendocrine neoplasms, rising from the parafollicular C cells.
- Secrete calcitonin, the measurement of which plays an important role in the diagnosis and postoperative follow-up evaluation of patients (If it increase after treatment this may indicates recurrence, so investigation should be reestablished).
- Are sporadic in about 70% of cases and the remaining 30% are *familial* cases.
- Note: Both familial and sporadic forms demonstrate activating *RET* mutations.

Calcitonin functions



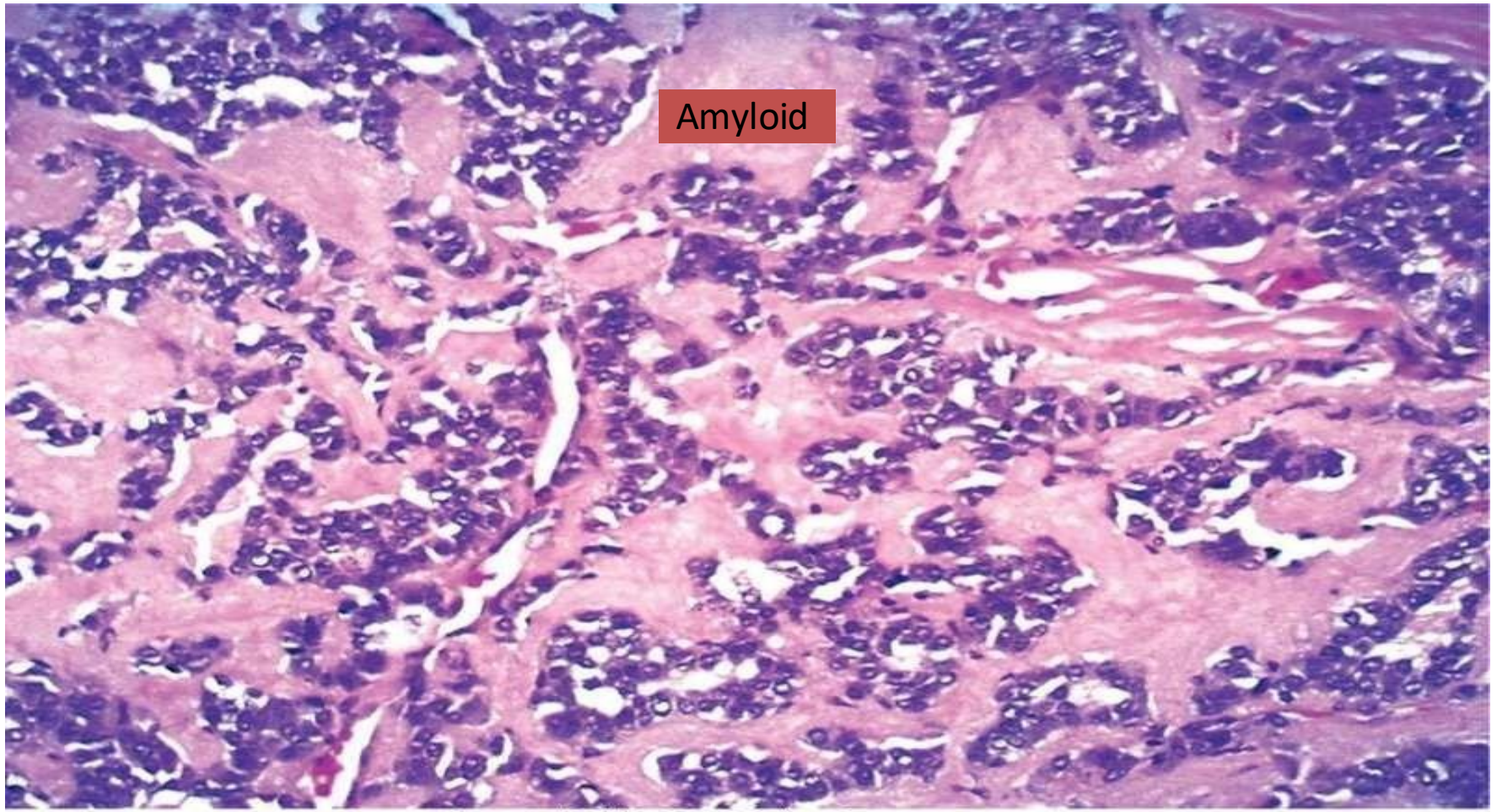
4. Medullary Carcinoma

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

- Amyloid: Any Extracellular accumulation of proteins & is several, chemically different proteins (not specifically calcitonin! , e.g. Aβ in Alzheimer's disease & Transthyretin in heart amyloidosis) that share similar physical characteristics (all are Beta pleated sheets & non-branching fibers). They can accumulate and form **pink** material called **amyloid**. See next pic.

Medullary carcinoma

Using H&E can't identify whether it is calcitonin, edema, fibrin, etc. So, a specific stain should be used to confirm that it is calcitonin – see next two slides.



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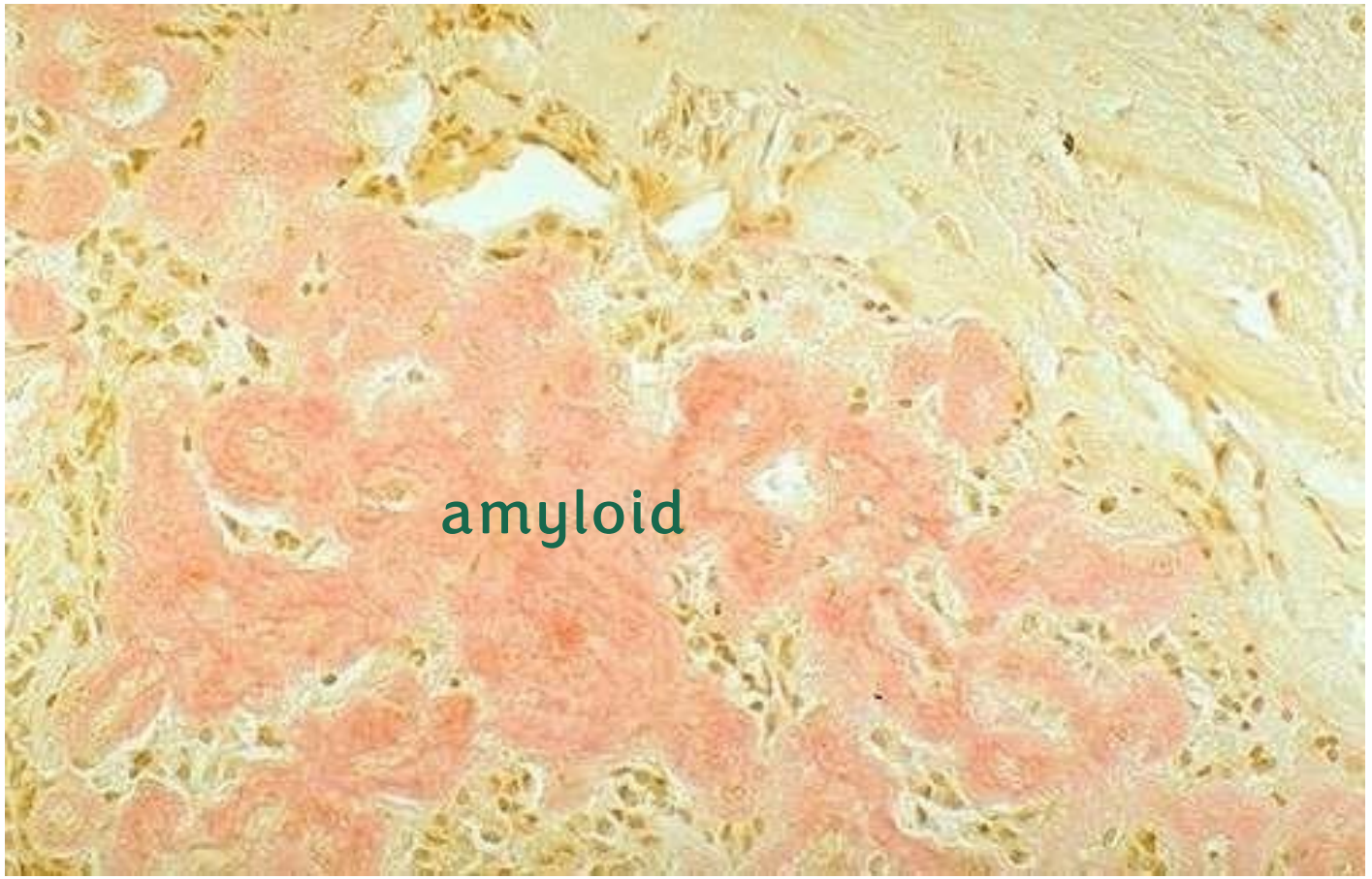
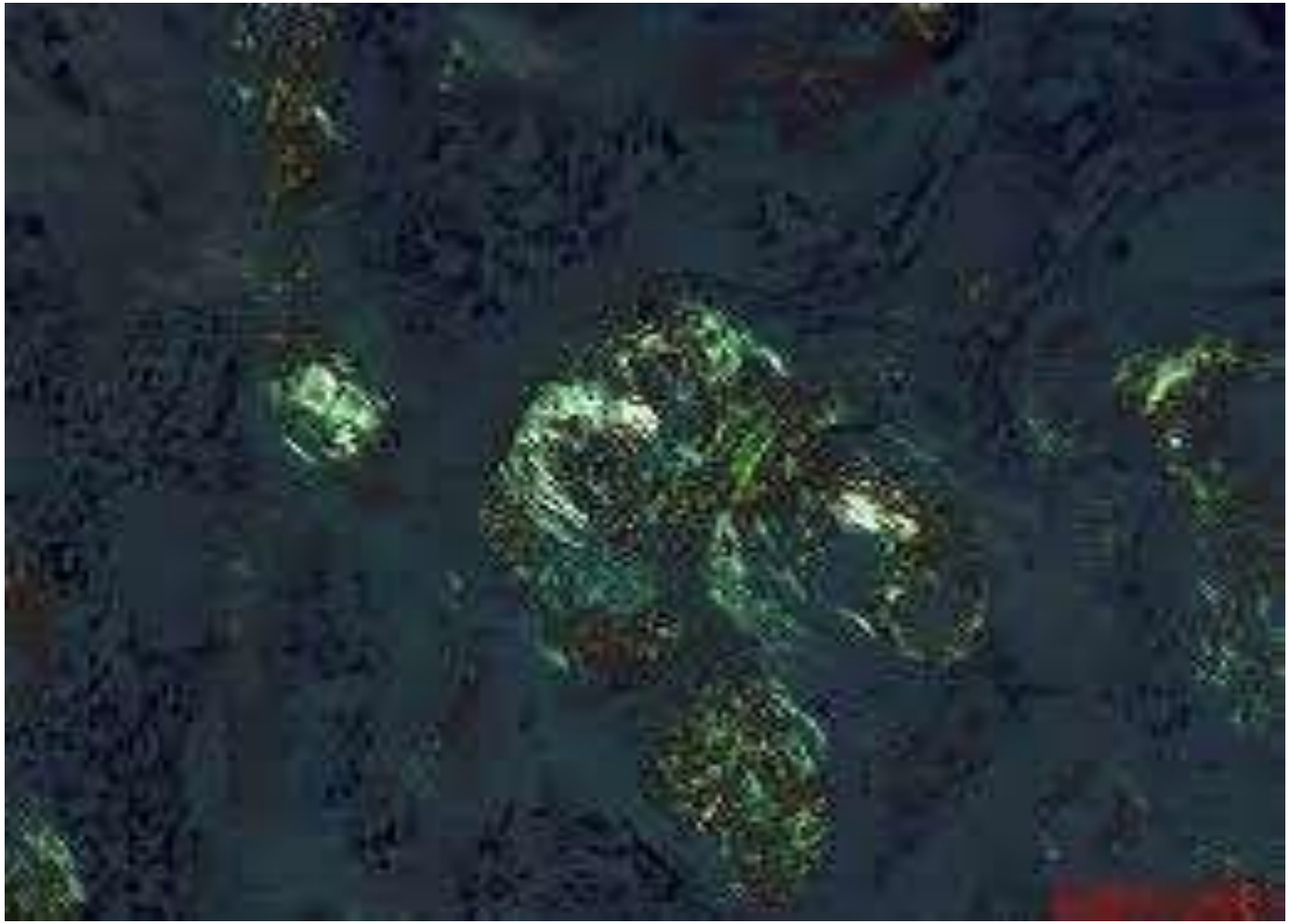
Very important (:

Amyloid stains with **Congo red stain**

Common exam question: which tumor is characterized with amyloid? Medullary carcinoma



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

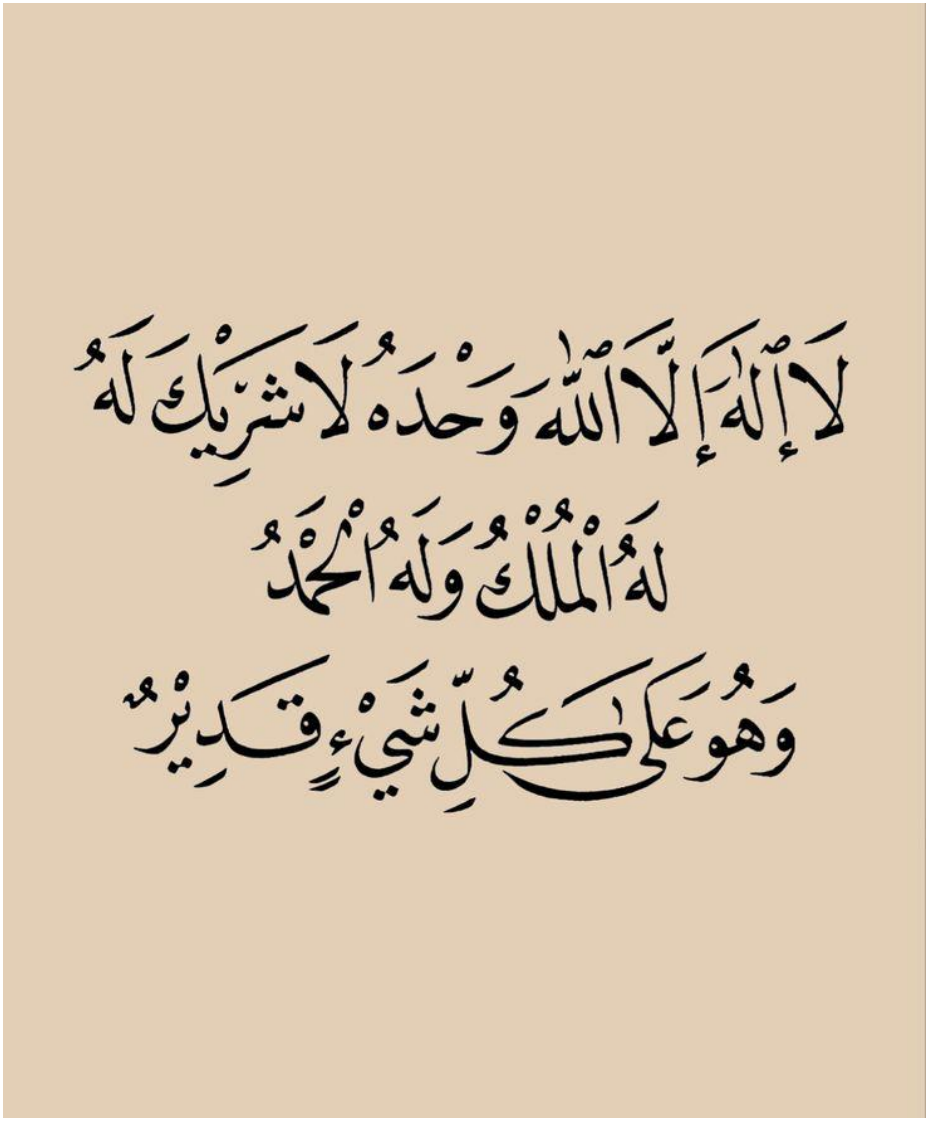
The patient has a long-standing history of Hashimoto’s thyroiditis, followed by a sudden worsening of symptoms, such as hoarseness of the voice and enlargement of the neck.


Thank you!

Pathology Quiz 3

Scan or click on it

رسالة من الفريق العلمي:



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			