The Endocrine System

☑ Sheet ☐ Slide ☐ Handout

Number:	3
Subject:	Thyroid diseases-2
Done By:	Bushra Arafa Zayed
Corrected by:	Hashim Ahmad Mohammad
Doctor:	Tariq Al-Adily

Date:

Price:

- The sheet was written according to record of section 1.
- Some points were not written in the exact order as the record.
- Everything in the slides, including the pictures, is mentioned in the sheet.
- Topics of the lecture:
  - Diffuse and multinodular goiter
  - Tumors of the thyroid:
    - Follicular adenoma.
    - Papillary carcinoma.
    - Follicular carcinoma.
    - Medullary carcinoma.
    - Anaplastic carcinoma.

❖ Diffuse and multinodular goiter:

- The pervious diseases of the thyroid cause either hypothyroidism or hyperthyroidism. This disease could cause any one of them.

- Reflects impaired synthesis of thyroid hormones. There is some **enzymatic deficiency** or there is a decrease production of the hormones at the **enzymatic level**.
- Commonly caused by iodine deficiency, especially in countries where table salt is not supplied with iodine.
- So at the beginning there is hypothyroidism but the body still normal.
  (Low T3 → more TSH → more thyroid hormones and enlarged gland → this rise in hormone levels is enough to compensate for the initial hormone deficiency).

- This will lead to compensatory rise in TSH (to compensate for the deficiency in the thyroid hormones → causing hypertrophy & hyperplasia of follicular epithelium → goiter (enlarged thyroid) is formed → then it will go back to the euthyroid level.

Remember: TSH has secretory effects (increases the synthesis and secretion of thyroid hormones) and trophic effects (increases the number of cells and causes conversion of the low-secreting cuboidal cells into a more columnar better-secreting cell type).

- There are two settings regarding the disease:
  - **Endemic goiter:** In the past, due to the difficult access to iodine, the disease was endemic in many countries. Nowadays iodine is available in the table salt in most of the world, so it is only endemic in a few countries; especially those which are away from the sea (i.e. in areas where soil, water and food contain little iodine (Himalaya, central Asia and Andes). So, in general, the disease nowadays has much lower incidence.

Euthyroid is the state of having normal thyroid gland function.

    - Note: Endemic means that 10% or more of population has the disease and it is persistent (fixed percentage, not changing with time).

  - **Sporadic goiter**: mostly idiopathic (no obvious cause. Unlike the cases where the disease is endemic the cause is usually unknown).
  - Other risk factors: excessive calcium intake, cabbage, cauliflower intake, true enzymatic deficiency (appears early in life, might develop in the childhood).
  - Enzymatic deficiencies are extremely uncommon.

- **Morphology of the disease:**
  - **Early stage**: there is an increase in the TSH → so diffuse goiter will develop (the entire thyroid is enlarged symmetrically and homogenously), similar to Grave's disease.

  - When **euthyroid status** is reached: TSH decreases and goes back to normal → no more activation of the follicular epithelium, so they become small and flat, with predominance of colloid. In other words, the cells are small and flat and the follicle is larger than normal and this is called colloid nodule. See Figure 1.

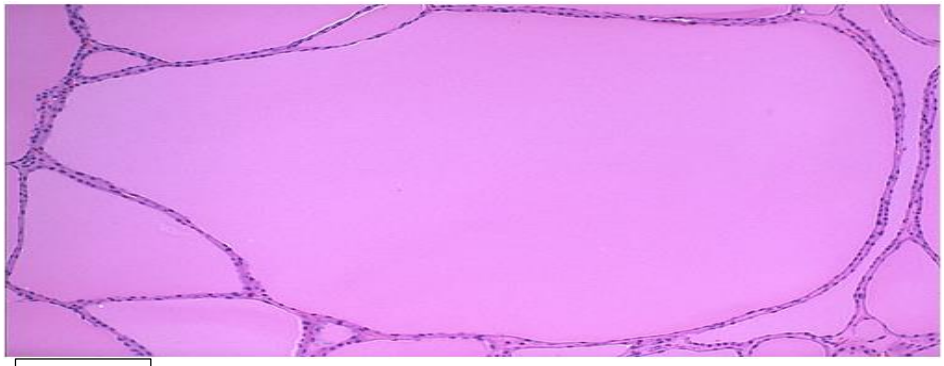


Figure 1

- But this disease is **persistent**, so after the euthyroid state, hypothyroidism state will return because we have persistent deficiency in the first place. So there will be cycles of **hypothyroid** and **euthyroid** statuses. And this leads to variation in the size of the thyroid.

- **Normally:** follicular epithelial cells are heterogeneous in response to TSH (as some cells have more receptors than others). So with repeated attacks:

- **Proliferatio**n of the cells is **variable** in size.
- Damage will occur producing **features of injury:**
  - ✓ Fibrosis.
  - ✓ Hemorrhage.
  - ✓ Cystic degeneration (empty spaces in the gland).
  - ✓ Calcification.

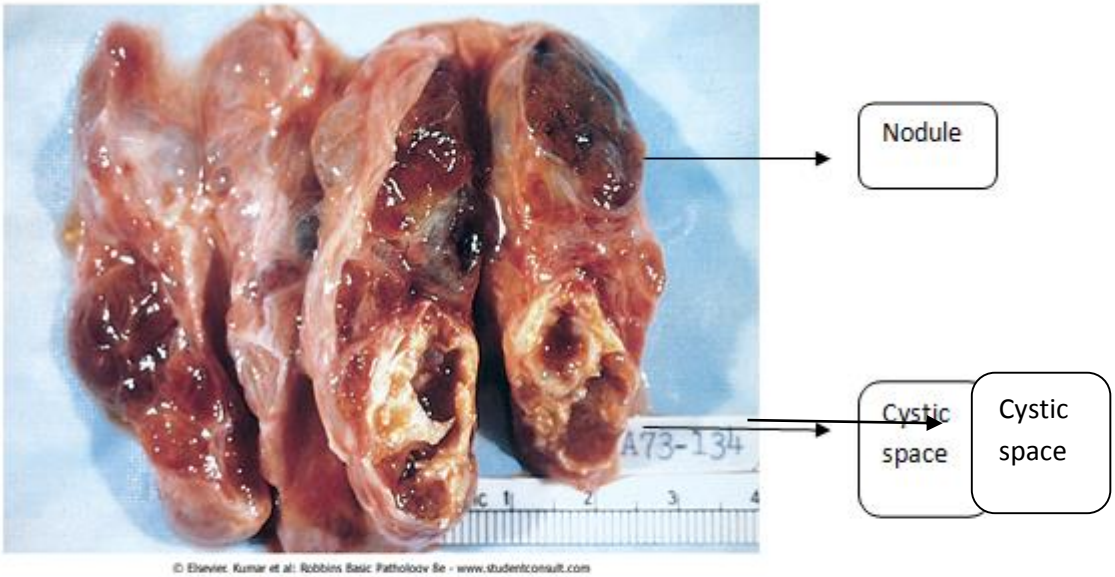
  → Goiter is irregular, some nodules are small while others are large, so it is called multinodular goiter.

- In some cases, one of the nodules may have a lower threshold to stimulation by TSH → so it becomes over-active, autonomous, secretes excess amounts of the thyroid hormone (thyroxine) and becomes dominant in the gland → so the patient will develop **Hyperthyroidism**. In this case, it is called **toxic nodule**.
- **NOTE:** In radiology, usually in the diagnosis of the thyroid disease, radioactive iodine is used. In the case of the toxic nodule, the gland is going to take a lot of the injected iodine and it appears very obvious.

- **At the molecular level,** some patients have **monoclonal** nodules like cancer but they don't progress. But most patients have **polyclonal** nodules. So monoclonality does **NOT** define cancer in this disease.

- **Clinically:**
  - The main complaint is mass in the neck (cosmetic). So, the patient comes because of the thyroid growth that increases with time to become bigger and bigger NOT from the thyroid status. In some cases the mass grows and reaches the mediastinum and causes **cancer-like** effects including:
- Stridor. صوت صرير
- Dysphagia.
- Compression of vessels.

- **Plummer syndrome: (Toxic Multinodular Goiter)**
  - It occurs when toxic nodule is formed and produces excess amounts of the thyroid hormone causing hyperthyroidism at the end, as mentioned before. Unlike Graves disease, this is not associated with ophthalmopathy and dermopathy.
- NOTE: remember that most patients have either Hypothyroidism or Euthyroid. So in this disease the status of the thyroid gland can be one of the 3 statuses**: HYPO, HYPER (few cases) or NORMAL** thyroid status.



The gland is coarsely nodular and contains areas of fibrosis and cystic change. Note the brown gelatinous colloid characteristic of this condition (colloid goiter).

❖ **Tumors of the thyroid gland:**

- Tumors of the thyroid, either benign or malignant, 99% of them are **non-functional** in which the thyroid's function is normal. They are called in this case **cold nodule** because if they were injected with radioactive iodine they won't take it up. So not taking iodine up is a suspicion of a tumor. They are opposite to the toxic nodule, which is not neoplastic.

- **Follicular adenoma:**

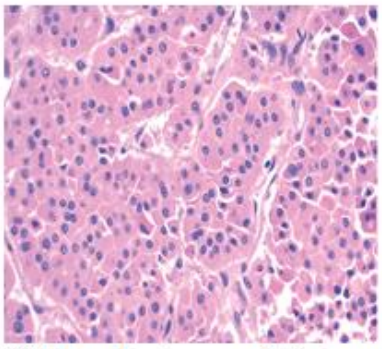
- Benign neoplasm of follicular epithelium, it is the **ONLY** benign tumor of the thyroid.
- As the name implies it arises from the follicular epithelial cells
- Solitary
- Mostly non-functional (cold nodule)
- Might be difficult to distinguish from hyperplastic nodule (toxic nodule) or carcinoma (especially the follicular carcinoma) in morphology. Morphology is mentioned later in the sheet.

- **Pathogenesis:**
- Activating (Gain-of-function) somatic mutation in either TSH receptor **or** α-subunit of G_s → causing overproduction of cAMP → cell growth and mitosis.
- **Rarely**, can be functional and produces hyperthyroidism, less than 1%.
- 20% of cases have **RAS** mutation (also present in 50% of follicular carcinoma cases) → So some cases of the follicular adenoma may **transform** into carcinoma.

- **Morphology:**
- Solitary
- It is benign, so it will be: well demarcated mass with intact thin capsule (not present in hyperplastic nodules)
- Microscopically: uniform follicles contain colloid distinct from the rest of thyroid, cells are uniform →So they look like the **normal** thyroid.
- Sometimes cells show a degree of metaplasia, more specifically, Hurthle cell change. It is called in this case **Hurthle cell adenoma.** But this change has **no significance** except in morphology.
- Atypia might be present, but does **not** mean malignancy.

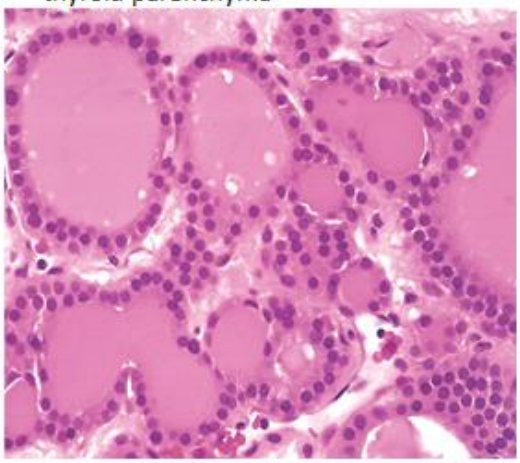
- NOTE: Atypia has no significance in the endocrine system like other systems. While invasion is very important and significant, as if there is any invasion to the capsule this means that there is a carcinoma. Thus, in the endocrine system, **invasion is the definite definition of cancer**.

***If capsular invasion is present → follicular carcinoma**



Hürthle cell adenoma. A high-power view showing that the tumor is composed of cells with abundant eosinophilic cytoplasm and small regular nuclei.

Well-differentiated follicles resemble normal thyroid parenchyma



- **Thyroid carcinoma:**

- Rare
- Occurs more commonly in women (estrogen receptors), like the other thyroid diseases.

Note: the relation between estrogen receptors and the thyroid cancer incidences is not fully understood until now. A lot of studies have been published regarding this subject.

- Mostly in the middle aged people. But like any cancer it may occur at any age, so old and pediatric cases might occur.
- Risk factor: **radiation**.
- All of the thyroid carcinoma types are derived from the follicular epithelium, except for **medullary** carcinomas (C-cell).

- Types of the thyroid carcinoma:

1. Papillary carcinoma (75-85%), most common
2. Follicular carcinoma (10- 20%)
3. Medullary carcinoma (5%)
4. Anaplastic carcinomas (<5%), least common

1. Papillary carcinoma:

- Most common thyroid cancer
- Arise at any age with peak at the middle age
- Risk factor: History of previous **ionizing** irradiation like nuclear radiation, not X-ray.
- NOTE: In Chernobyl there was a massive increase in the incidence of papillary carcinoma due to an explosion of Chernobyl nuclear power plant that released large quantities of radioactive particles into the atmosphere, which spread over much of the western USSR (Union of Soviet Socialist Republics) and Europe.
- Like any cancer of the thyroid, patient comes due to **painless mass** in neck, not because of the thyroid function.

- **Solitary or multiple** which is an exception (most neoplasms are solitary).

- Commonly associated with local LN metastasis, but this **does not affect the prognosis**.
- Indolent disease (10 year survival > 95% , by just removing the thyroid.
- It is the best known cancer in the prognosis and treatment.

➢ **Pathogenesis:**

**NOTE: it is important to know the pathogenesis at the molecular level, because at this time medicine focuses on the mutant gene and tries to inhibit it. So you should know the mutant genes very well.*

- Two different pathways, both of them end by activating *mitogen activating protein* (MAP) kinase signaling pathway that activates cell proliferation.
- The two pathways are :

1- BRAF pathway: Important

✓ 1/3 of the cases have BRAF gene mutation, activating MAPK.

- ✓ BRAF mutations are found in other types of human cancers like multiple myeloma, and some leukemia's.

2- **RET gene pathway**:

- ✓ 20% of the cases have a mutation in RET gene rearrangement (same locus but different sequence), so the new sequence will create a new gene (ret/PTC) → which activates RET protein and MAPK.
- ✓ PTC = papillary thyroid carcinoma.

- 10% Neurotropic tyrosine kinase receptor1 (NTRK1) mutation (not that important)

- **Morphology:**
- Papillary carcinoma has very special morphology. And the diagnosis depends on the morphology.

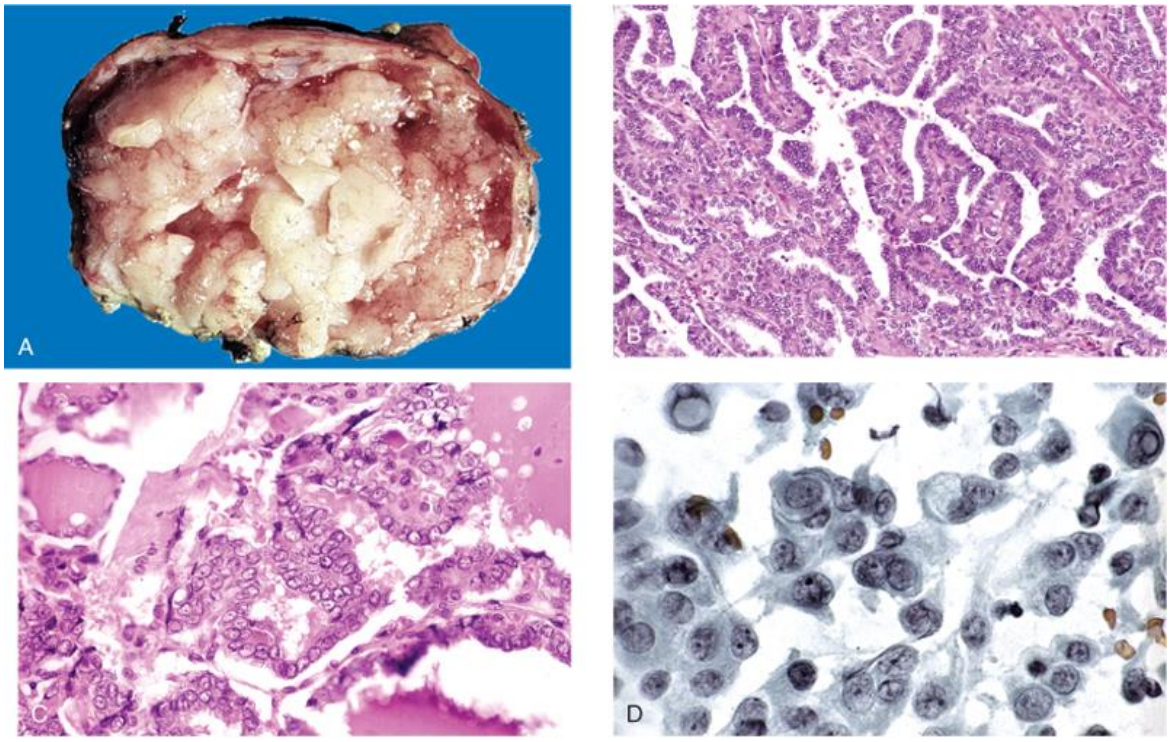
- Its morphology is not related to the mutant genes. It is not even known why it has such morphology, but it's still very important and specific.
- Grossly: well circumscribed, sometimes even encapsulated like the benign tumors. Remember it is an indolent disease and not aggressive.

- Microscopically:
  - **A.** Special **nuclear features that give this carcinoma a very special morphology**:
    - ***1- Optically clear nuclei:***
      - ✓ Called ground glass or Orphan Annie eye:
      - ✓ The nuclei are very white in color instead of blue like in the normal cases.
      - ✓ Orphan Annie is a cartoon character was drawn with special eyes like the nuclei in the papillary carcinoma.
    - *2-* ***Nuclear grooves****:*
      - ✓ Secondary to the invagination of the cytoplasm into the nuclei in a sharp way
      - ✓ Appears at low magnification like a line
      - ✓ Called coffee beans or pseudoinclusions

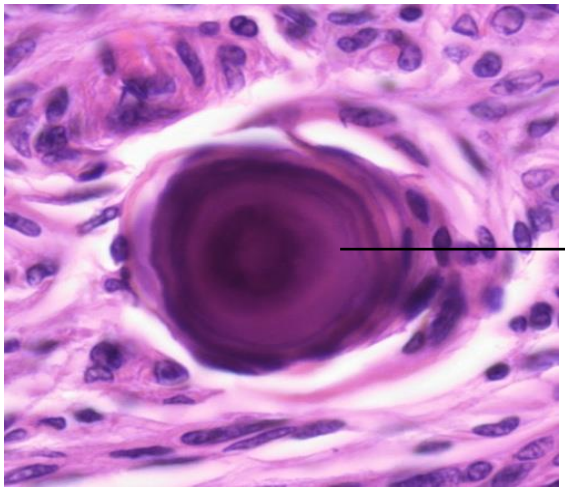
True papillae: projection of the cells with a fibro-vascular core.

Remember in Grave's disease the papillae lack a fibro-vascular core, as the papillae are formed because of hyperplasia and crowding.

B. **Papillary** architecture: there are true papillae which have blood vessels to support malignant cells.
C. **Calcification:** as cells at the tip of the papillae have least blood supply, so they die and are then calcified. This calcification forms masses known as **psammoma** bodies.
D. **Cysts** are common: cysts can develop in any tumor; benign or malignant.



- Regarding the figure:
  Papillary carcinoma of the thyroid. **A,** A papillary carcinoma with grossly discernible papillary structures. This particular example contained well-formed papillae (**B**), lined by cells with characteristic empty-appearing nuclei, sometimes termed "Orphan Annie eye" nuclei (**C). D,** Cells obtained by fine-needle aspiration of a papillary carcinoma. Characteristic intranuclear inclusions are visible in some of the aspirated cells.

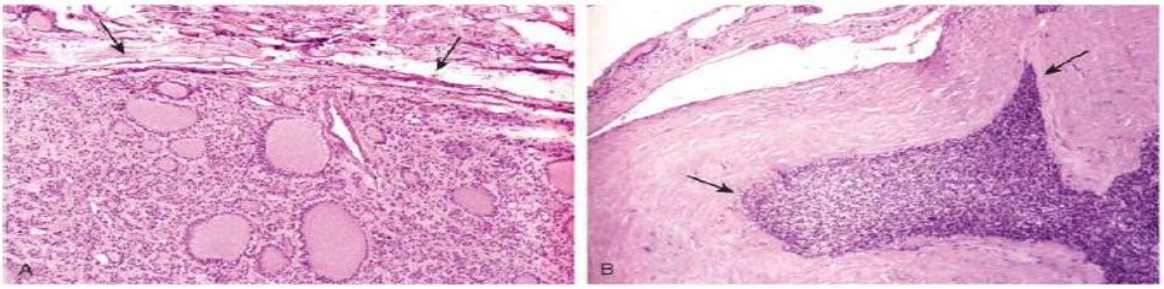


Psammoma body: concentric calcification

- **Follicular carcinoma:**
  - Second most common cancer
  - Older age than PTC
  - Associated with iodine deficiency in some cases but not most of them
  - **RAS mutation in 50%**
  - Microscopically:
    - ✓ Normal looking follicles
    - ✓ May show Hurthle cell change
    - ✓ **Invasion to capsule, lymphatics or blood vessel**

      >>>> So it looks like follicular adenoma except that there is **invasion**

  - Remember: invasion defines the malignancy.



- Capsular invasion in follicular carcinoma. Evaluating the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas. In adenomas (**A**), a fibrous capsule, usually thin but occasionally more prominent, surrounds the neoplastic follicles and no capsular invasion is seen *(arrows);* compressed normal thyroid parenchyma is usually present external to the capsule *(top).***B,** In contrast, follicular carcinomas demonstrate capsular invasion *(arrows)* that may be minimal, as in this case, or widespread with extension into local structures of the neck

- **Medullary carcinoma:**

- Neuroendocrine neoplasm, arises from **parafollicular** cells (C-cells) that secrete calcitonin.
- Increased blood level of calcitonin (but no hypocalcemia or any change in calcium level)
- Sporadic in 80% of cases, mostly in old aged people
- 20% are **familial**
- Occurs at a younger age (appears earlier in life), aggressive disease
- It could be one of the two following cases:

1- **Familial medullary thyroid carcinoma**: these people develop thyroid carcinoma only without other cancers; it is inherited either maternally or paternally.
2- **Multiple Endocrine Neoplasia** (MEN SYNDROME).

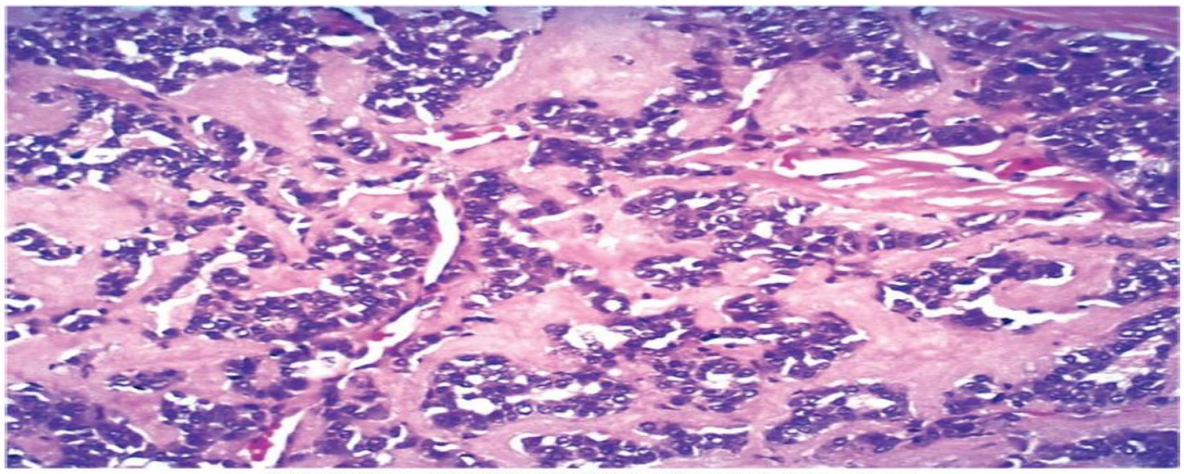
- *REMEMBER: MEN syndrome is one of the causes of pituitary adenoma.*

- There is a **RET gene mutation**
- Note that in PTC, RET gene has undergone a **rearrangement** with PTC gene. While in medullary carcinoma the gene itself is **mutated** without any rearrangement.

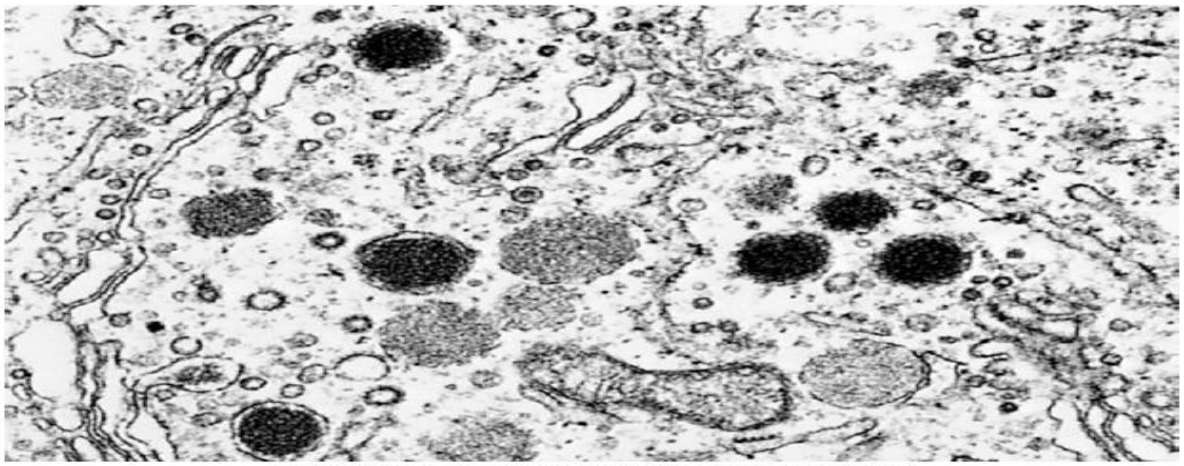
Amyloid: is a protein that has a specific feature and structure, deposited in the tissues when diseased causing physical damage. It is positive to Congo red stain.

- **Morphology:**
- Solitary tumor (sporadic) or multiple (familial, because they have inborn mutations, so they will develop multiple growths.
- Microscopically: C-cells when they are malignant they still look like **normal** (polygonal) or sometimes they become **spindle cells**. So they have a **variable** morphology.
- **Secrete amyloid** (derived from calcitonin) which is positive for Congo red stain. This is the most important morphological feature. Used in diagnosis.
- C-cell hyperplasia in non-tumorous areas: they appear crowded without follicles.
- Note that at the same time we have areas that represent tumors and others that are only hyperplastic.

- Electron microscopy: membrane-bound granules containing calcitonin.



- Medullary carcinoma of the thyroid. These tumors typically contain amyloid, visible here as homogeneous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells.



Electron Microscope

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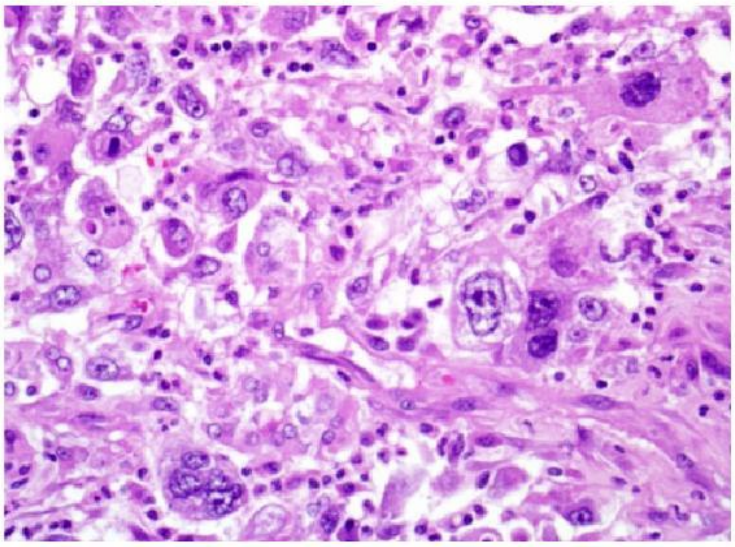
- **Anaplastic carcinoma:**

Remember P53 is the guardian of the genome. Once it is mutated, other mutation will accumulates in the cell.

- Very aggressive, one of the worst human cancers
- Old age
- History of thyroid diseases: multinodular goiter or PTC
- P53 mutation is always there.
- Rapid growth within few weeks causing severe destruction
- Death within one year
- Cells are anaplastic, so they will be large, epithelioid or spindle, and pleomorphic.

Anaplastic thyroid carcinoma: **bizarre cells.**



Sorry for any mistake

Wish you all best of luck

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