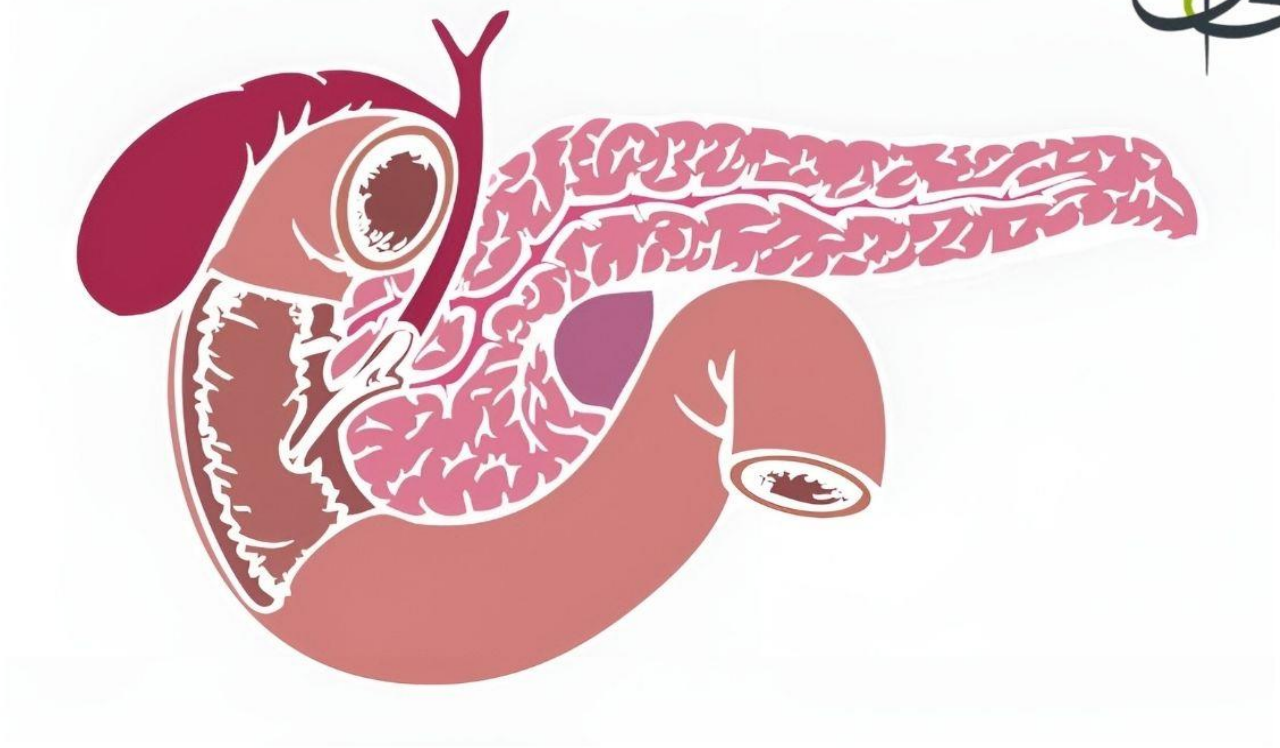
Endocrine system

Sheet 4

Pathology



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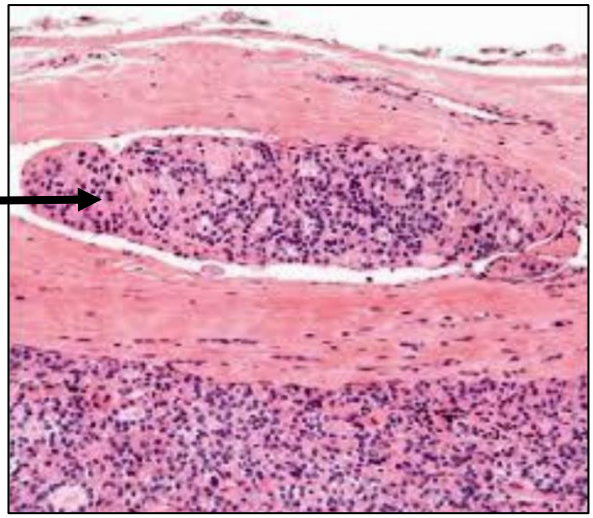
FOLLICULAR CARCINOMA

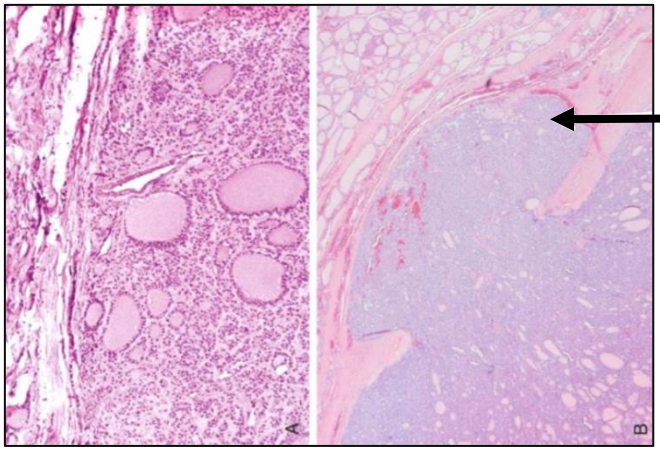
- More common in women, 40-60 years.
- common in iodine deficient regions.
- Solitary cold nodule (solitary cold nodules carry high risk as mentioned previously).
- **Hematogenous spread** to lung, liver, brain, and **bone** (one of the "bonophilic" tumors along with lung, prostate, renal, breast cancers as well as HCC).
- More aggressive than papillary carcinoma, 50% of patients die within 10 years.

- **Capsular and vascular invasion is the distinguishing feature from follicular adenoma**; Follicular neoplasms are differentiated only by histology. The whole lesion is surgically removed by either a complete thyroidectomy or a lobectomy and is sectioned and evaluated microscopically. For a diagnosis of a follicular carcinoma to be made, capsular invasion and vascular invasion of the capillaries within the capsule or outside of it (NOT inside the lesion) must be seen. It is often difficult to see definite invasion and such cases are termed *minimal deviation follicular carcinoma* and are monitored.
- **Cytology cannot differentiate between the two**. An FNA of a follicular neoplasm shows a follicular growth pattern, no papillary features but doesn't distinguish a follicular adenoma from a carcinoma as the capsule cannot be examined so it needs to be followed up by histological examinations.

Vascular invasion

The figure shows a vein invaded by a follicular neoplasm. A true invasion can be distinguished by certain clues one of which is the adhesion of the tumor to the wall of the vessel which is sometimes associated with thrombosis.





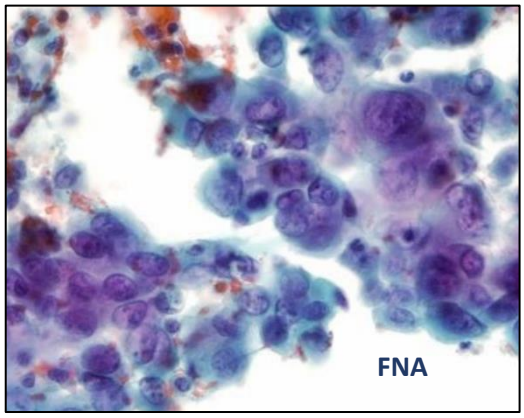
Capsular invasion

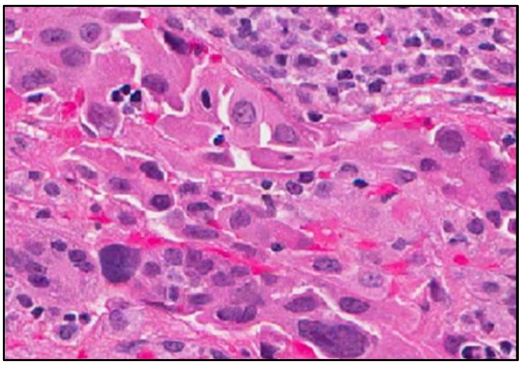
Mushroom shaped protrusion through the capsule.

ANAPLASTIC CARCINOMA

- Not common, less than 5% of thyroid malignancies.
- Undifferentiated carcinoma.
- Very aggressive, 100% mortality in less than a year.
- Patients are usually older than 65 years.
- 25% have history of previous well-differentiated thyroid carcinoma. Indicated by finding an adjacent well differentiated carcinoma while sectioning as well as both follicular carcinoma for instance and anaplastic thyroid carcinoma having RAS mutations.

Anaplastic features (variable sizes of cells and nuclei, abnormal mitosis, hemorrhage, necrosis, etc…) detected in histology and cytology.



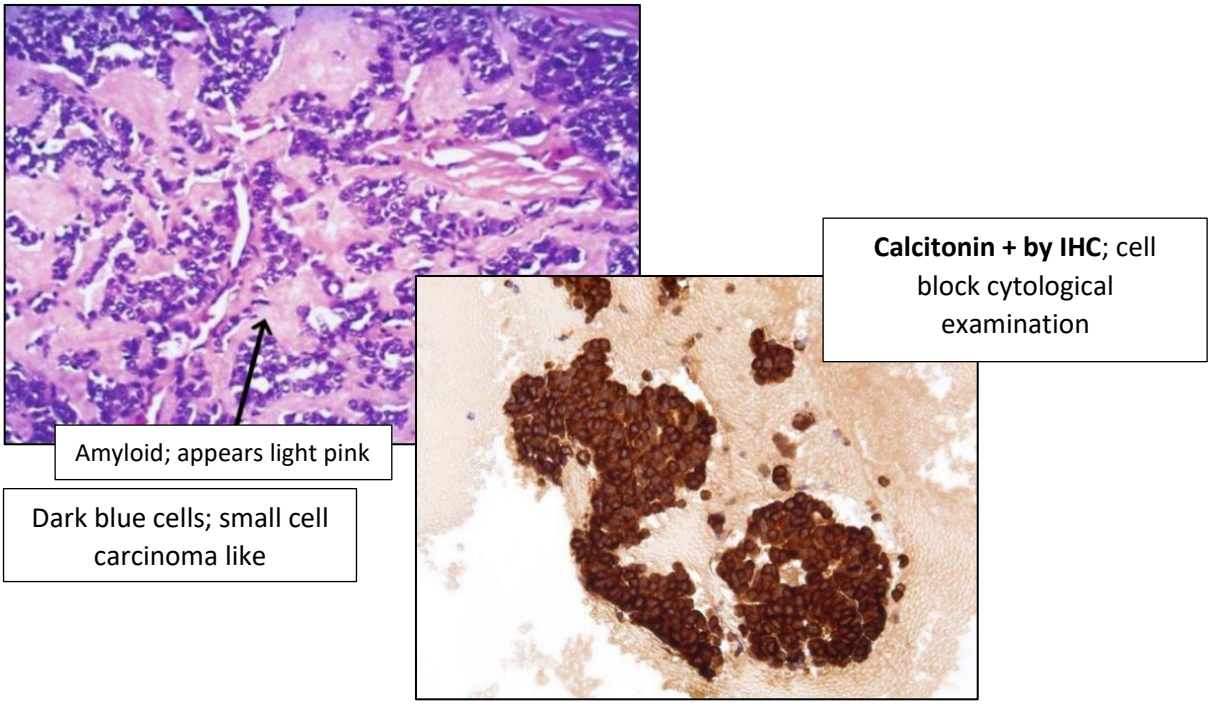


- An anaplastic thyroid carcinoma most commonly presents as a rapidly enlarging anterior neck mass in elderly patients. FNA is done, bizarre cells are detected, and immunostaining is done to determine the origin of the cells to differentiate it from other anaplastic cancers.
- **Sometimes severe necrosis occurs leading to neutrophilic infiltration that can be mistaken for an abscess upon evaluation.**

MEDULLARY CARCINOMA

- Arise from C cells **(parafollicular cells)** that secrete calcitonin, **↑calcitonin and ↓Ca^{2+} (hypocalcemia)**.
- 70% sporadic, 50-60 years. 30% familial, younger age groups (MEN 2A&B).
- **RET receptor tyrosine kinase mutations, specific for medullary thyroid carcinoma.**
- Treatment is total thyroidectomy.
- Multicentric, contain amyloid.
- Since almost third of the cases are associated with familial history and syndromes, all family members of the patient must be screened for RET mutations. **RET +ve family members require prophylactic thyroidectomy.**

- **Medullary carcinoma has specific cytological features.** Immunostaining using different stains for **calcitonin**, thyroid transcription factor (TTF-1) which stains both thyroid and lung cells, thyroglobulin which is specific for the thyroid, and **amyloid (Congo Red stain, examined under the polarizing microscope, amyloid looks apple green)**



- NOTES:
- Follicular carcinomas DO NOT arise from adenomas. Each one is caused by different mutations.
- **B cell non-Hodgkin lymphoma** of the thyroid is rare, and its risk increases with Hashimoto thyroiditis. Resembles B-NHL in other locations.

PARATHYROID GLAND

- PTH is secreted by Chief cells and is controlled mainly by free Ca^{2+} level in serum (feedback mechanisms), minimal effect by tropic hormones.
- Disorders include Hyperparathyroidism, Hypoparathyroidism and tumors which rarely cause mass effects, so it does not affect swallowing or breathing and is more functioning unlike thyroid tumors.

- Functions of PTH aim to increase blood calcium levels:

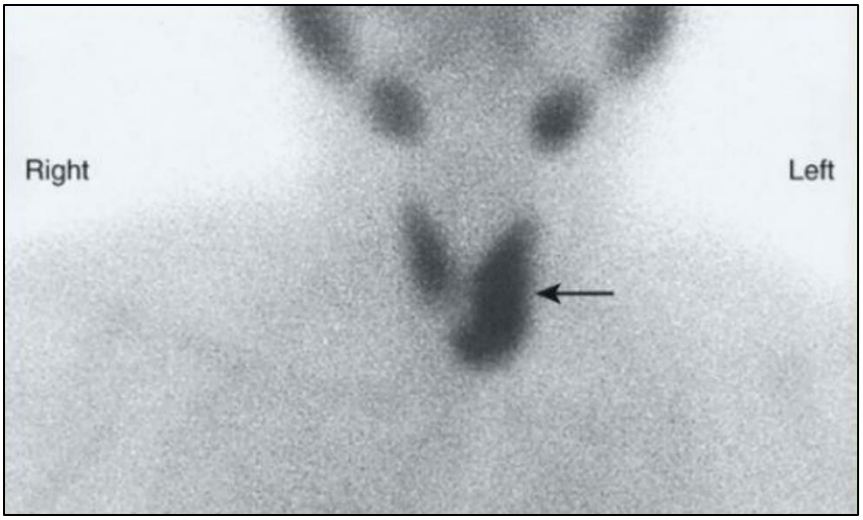
– Reabsorption of Ca from renal tubules.
– Excretion of PO4 into urine.
– Vit D conversion to active form.
– Stimulates osteoclast activity on bone resorption.

HYPERPARATHYROIDISM

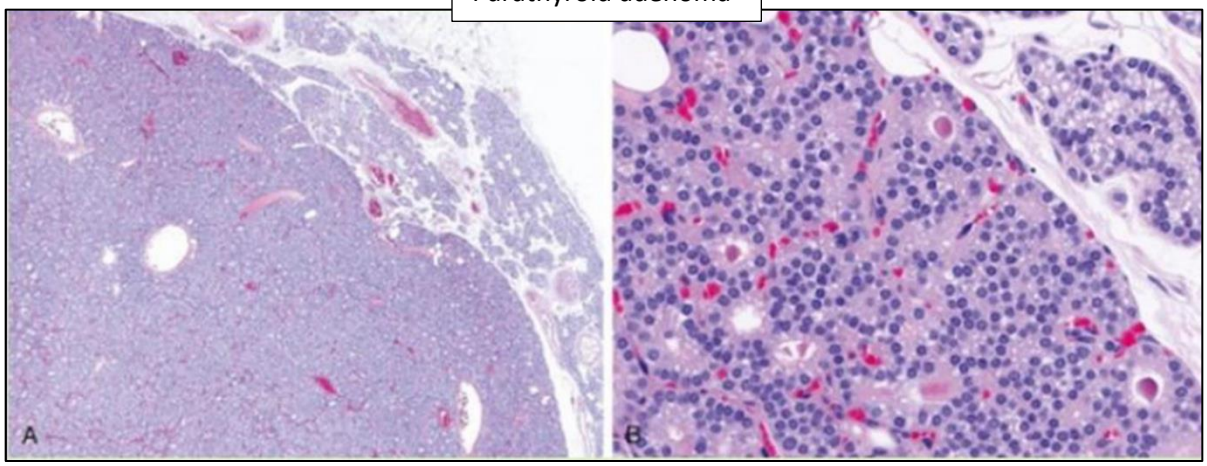
- Primary, secondary and tertiary.
- Severe hyperparathyroidism causes: **Osteitis fibrosa cystica**, **Brown tumor of bone** (not a real tumor characterized by bleeding and repair as well as cyst formation), **nephrolithiasis**, **nephrocalcinosis** and **metastatic calcifications.**
- Hyperparathyroidism must be treated, **mainly surgically**.
- **Primary HPT** caused by:

– **Adenomas (usually in one gland) (85-95%)**, Hyperplasia (usually in patients with chronic renal failure, in all four glands) (5- 10%), rarely; carcinoma (1%).

– Mutations: Cyclin D1 gene on chromosome 1 or MEN1 mutations (adenoma and hyperplasia of the parathyroid are a part of MEN syndromes).



Parathyroid adenoma



CAUSES OF HYPERCALCEMIA

Increased PTH	Decreased PTH
Hyperparathyroidism	Hypercalcemia of malignancy
Primary (adenoma > hyperplasia)*	Osteolytic metastases
Secondary†	PTH-rP–mediated
Tertiary†	Vitamin D toxicity
Familial hypocalciuric hypercalcemia	Immobilization
	Drugs (thiazide diuretics)
	Granulomatous diseases (sarcoidosis)

Notes:

- ✓ You always check PTH levels in cases of hypercalcemia.
- ✓ Both secondary and tertiary hyperparathyroidism are associated with chronic renal failure. However, of a much longer duration in tertiary hyperparathyroidism (10-15 yrs) and of a shorter duration in secondary hyperparathyroidism (3-5 yrs) which is considered the main distinguishing feature along with serum phosphate levels.
- ✓ Hypercalcemia with increased PTH is rarely caused by *familial hypocalciuric hypercalcemia*; an inherited disorder that causes abnormally high levels of calcium in the blood (hypercalcemia) and low to moderate levels of calcium in urine (hypocalciuric).
- ✓ PTH-rP-mediated: parathyroid hormone related protein is secreted by some type of malignancy like lung cancers or paraneoplastic syndromes, causes an increase in serum calcium levels which in turn inhibits PTH secretion.

Hyperparathyroidism classification

Different causes and features of hyperparathyroidism - raised parathormone (PTH).

	primary	secondary	tertiary
pathology	Hyperfunction of parathyroid cells due to hyperplasia, adenoma or carcinoma.	Physiological stimulation of parathyroid in response to hypocalcaemia.	Following long term physiological stimulation leading to hyperplasia.
associations	May be associated with multiple endocrine neoplasia.	Usually due to chronic renal failure or other causes of Vitamin D deficiency.	Seen in chronic renal failure.
serum calcium	high	low / normal	high
serum phosphate	low / normal	high	high
management	Usually surgery if symptomatic. Cincacalcet can be considered in those not fit for surgery.	Treatment of underlying cause.	Usually cinacalcet or surgery in those that don't respond.

NICE have issued guidance for the use of cinacalcet in what they call refractory secondary hyperparathyroidism which is classified as tertiary hyperparathyroidism in this tblable. http://www.nice.org.uk/TA117

HYPOPARATHYROIDISM

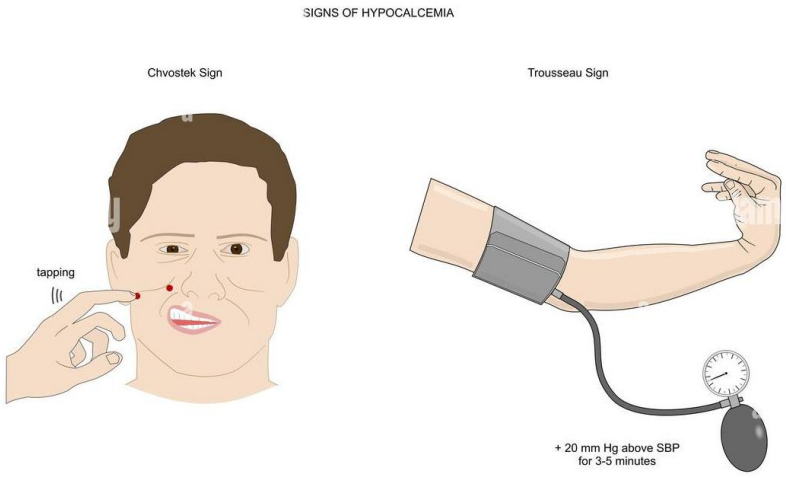
↓PTH = ↓Ca^{2+}

Causes:

Thyroid surgery, parathyroid surgery, autoimmune, infiltrative, familial; rare, idiopathic; rare.

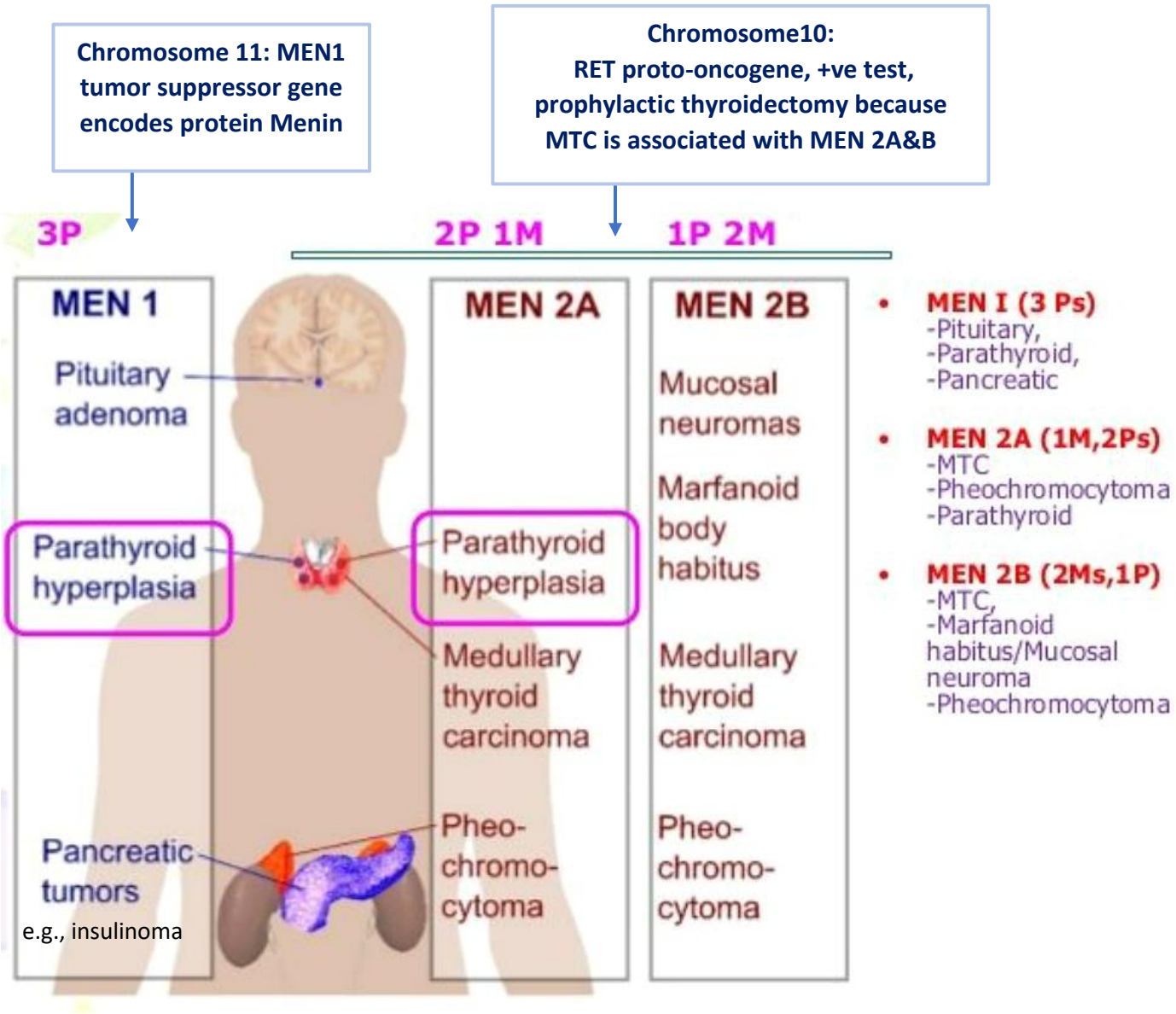
Hypocalcemia leads to:

- Tetany
- Chvostek sign (contraction of facial muscles after tapping facial nerve)
- Trousseau sign (induction of carpal pedal spasm;)
- Paresthesias, numbness (fingertips/perioral)
- Prolonged QT interval



MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES (MEN)

- Inherited disorders, proliferation or neoplasms of multiple endocrine organs.
- Younger age groups.
- Synchronous (tumors occur at the same time; within 6 months) or metachronous (at different times; more than 6 months) in multiple organs.
- **Often muti-focal in the same organ** creating difficulty in treatment.
- Often preceded by asymptomatic hyperplasia.
- **More aggressive than their sporadic counterparts.**


Chromosome 11: MEN1 tumor suppressor gene encodes protein Menin
Chromosome10: RET proto-oncogene, +ve test, prophylactic thyroidectomy because MTC is associated with MEN 2A&B
3P
2P 1M
1P 2M
MEN 1
Pituitary adenoma
Parathyroid hyperplasia
Pancreatic tumors
e.g., insulinoma
MEN 2A
Parathyroid hyperplasia
Medullary thyroid carcinoma
Pheo-chromo-cytoma
MEN 2B
Mucosal neuromas
Marfanoid body habitus
Medullary thyroid carcinoma
Pheo-chromo-cytoma
MEN I (3 Ps)
-Pituitary,
-Parathyroid,
-Pancreatic
MEN 2A (1M,2Ps)
-MTC
-Pheochromocytoma
-Parathyroid
MEN 2B (2Ms,1P)
-MTC,
-Marfanoid habitus/Mucosal neuroma
-Pheochromocytoma

GOOD LUCK

Questions:

A 20 year-old patient presented with a thyroid nodule and hypocalcemia. An FNA was done followed by IHC that was positive for calcitonin and amyloid.

1.What's the most likely genetic mutation leading to this condition:

a. RET.
b. RB.
c. P63.
d. RAS.
e. P53.

2. What's the proper management?

a. screen family members for similar mutations. And those with a positive test must have a prophylactic thyroidectomy.
b. total thyroidectomy.
c. the case is simple and is treated by calcium and vitamin D supplementation.
d. both a & b.
e. none of the above.

3. Which of the following thyroid diseases CANNOT be diagnosed by Fine needle aspiration (FNA)?

a. Papillary thyroid carcinoma.
b. Hashimoto thyroiditis.
c. Follicular carcinoma.
d. Thyroid cyst.
e. All diseases can be diagnosed by FNA.

4. All of the following combinations regarding thyroid tumors are correct EXCEPT:

a. Anaplastic carcinoma and TP53 mutation.
b. Medullary carcinoma and calcitonin production.
c. Follicular carcinoma and iodine deficiency.
d. Anaplastic carcinoma and good prognosis.
e. papillary carcinoma and lymph node metastasis.

answers: 1.a 2.d 3.c 4.d