**PARATHYROID GLANDS**

**(**Normally** 4 glands, each is 4x3x1.5**mm**, weight of all 4 glands is **117mg** in men & **131** mg in women**, = 1/8 of gram!**

**◙ H,**

(1) most of the glands composed of ***Chief cells**, which* vary from light to dark pink with H&E stains, depending on their glycogen content.

الخلايا الرئيسية ***Chief***

They contain secretory granules of *parathyroid hormone (PTH), and*

*(2)* ***Oxyphil cells,*** having acidophilic cytoplasm & are tightly packed with mitochondria, found singly or in small clusters.

من اسمها حمرا

يا ب

****Normally,** ***the activity of the parathyroid is controlled by the level of free (ionized) calcium in the bloodstream rather than by trophic hormones*** *secreted by the hypothalamus & pituitary.*

ال gonads +suprarenal+ thyroid تعتمد ال activity تبعتها على

***trophic hormones produced by pituitary***

*ال**parathyroid** عبارة عن exception لانه نشاطها يعتمد ويسيطر عليه اشي واحد يلي هو انه ما هو مستوى **free (ionized) calcium** يزيد يقل نشاطهاويقل انتاج ال PTH و يقل Ca يزيد الانتاج تبع ال PTH ويحفز خروج الكالسيوم من العظام يلي هو المخزن الاساسي للكالسيوم الى الدم*

**Decreased levels of free calcium stimulate the synthesis & secretion of PTH, which ↑ the level of free calcium, inhibiting further PTH secretion.

inhibiting further بس يزيد الكالسيوم بالدم ويرجع لحالته الطبيعية رح يعمل PTH secretion.

**Parathyroids abnormalities include both ▲hyper & ▼hypofunction.

## ▲ HYPERPARATHYROIDISM

**occurs in two major forms, ***primary*** & ***secondary,*** & less commonly, as ***tertiary*** hyperparathyroidism.

يا بكون اولي او ثانوي او ثالثي

### Primary Hyperparathyroidism

**Primary hyperparathyroidism is an <u>autonomous, spontaneous</u> overproduction of PTH

هي عملية ذاتية اولية لزيادة الهرمون

**is one of the **most common endocrine disorders,** & it is an important cause of ***hypercalcemia,***

***طبعا مهو كل ما زاد الهرمون بالدم رح يخرج الكالسيوم من مخازنه***

***عنا تلت اسباب تؤدي الى hyper*** عادهم مرتين :

in the following **frequencies** of occurrence:

(I) Parathyroid **Adenoma (A) - 80%,**

(II) **Primary hyperplasia** (diffuse or nodular) **-15%,**

**by itself <u>autonomous, spontaneous</u>** **فرط نمو الغدة**

(III) Parathyroid **carcinoma - 5%**

***Molecular Pathogenesis of Parathyroid Tumors (T)*

The two genes abnormalities commonly associated with parathyroid T are;

(1) *PRAD1* (*parathyroid adenomatosis gene 1*), is located on chromosome11q. The protein product of *PRAD1 is* cyclin D1. **Overexpression of cyclin D1 is common in parathyroid T (adenomas & carcinomas) as well as in hyperplasia**.

(2) T suppressor gene ***MEN1*** on chromosome 11q13, germ-line mutations of which are responsible for the MEN-1 syndrome.

*20% to 30% of parathyroid T not associated with the MEN-1 syndrome also demonstrate mutations of the *MEN1* gene.

يعني *MEN1* gene اما موجود ب syndrome نفسه او موجود ب ٢٠ ل٣٠ بالمية من بالاشخاص المصابين parathyroid T وما عندهم ال syndrome

**#Changes in** primary hyperparathyroidism are seen in :

شو التغيرات التي تحدث بكل انواع الثلاثة السابقة A + Ca + hyperplasia ؟؟؟

(I) in the **parathyroid glands**,

(II) in **other organs** affected by elevated levels of calcium.

☼*T of the parathyroid glands, unlike thyroid tumors, usually come to attention because of* ***excessive secretion of PTH rather than the local mass effects!***

***اذا فيه ورم بالغدة الدرقية المريض شكوى بتيجي من local mass effect والمريض بيجي يحكي انه عنده عقدة بالرقبة***

***بس هون هاد الاشي مستحيل لانها اصلا صغيرة ولو كبرت الف مرة ما رح تكون clinically apparent لذلك شكوي المريض او ال attention بتيجي بسبب excessive secretion of PTH يلي رح يؤدي الى hypercalcemia واذا ال A ما سوت PTH ما رح تحس فيها مطلقا ولا المريض رح يجي يشكي منها***

## (I) Parathyroid Adenoma (A)

**80% of primary hyperparathyroidism cases are caused by

a solitary parathyroid A**,**

**which, like the normal parathyroids, **may lie** in close proximity to the thyroid gland or in an ectopic site (e.g., the mediastinum).

اذا صارت ال A اما تكون موجودة بمكانها الاصلي يلي هو post to thyroid gland ٢ عاليمين ٢ عاليسار وتحت وفوق ولكن بعض الاحيان ما بتكون موجودة بمكانها الحقيقي تكون موجودة بمكان اخر وخاصة بمنطقة mediastinum

**#By definition** parathyroid A is

في خواص بنعرفها فيها

→ **single** (F20-19),

→ **well-encapsulated**

**زي ال thyroid A**

→ **soft tan nodule ( LIGHT BROWN in color )**

→ **0.5** to **5 gm**.

حكينا وزنها الاصلي هو ثمن غرام يعني اذا صارت ٥ غرام معناته تضاعفت ٤٠ حجمها الاصلي

**The remaining three glands are either normal in size or somewhat

→ **shrunken**, as a result of feedback inhibition by elevations in serum calcium.

جزء منها رح يزيد افراز الهرمون رح يؤدي الى زيادة الكالسيوم بالدم ممكن يعمل feedback على الجزء السليم وما يخليها تشتغل وتنكمش وممكن تضل بحجمها الطبيعي

نوتس على الصورة 9-20

بنشخص الحالة عن طريق

**Technetium-99-sestamibi radionuclide scan**

انتبه انه

Enlargement of size of one >>>> case of A

يعني بتكون وحدة

{In contrast to **parathyroid hyperplasia**, in which → **more than one gland** would demonstrate increased uptake}.

بتكون ٣ او ٤ او ٢

طب لي مهم هاد الحكي ؟ عشان تعطيك فكرة قبل ال surgery شو رح تشيل وحدة ؟؟ ولا كلهم ؟

تذكر انه A تمثل ٨٠ بالمية من حالات

و hyperplasia تمثل ١٥ بالمية

#◙ **H, of** parathyroid A **:**

→**Chief cells** which are larger & show greater 20 - F20 nuclear size variability than the normal chief cells. It is not uncommon to find bizarre & pleomorphic nuclei even within benign A (**endocrine atypia).**

**هاد حكينا عنه ب thyroid يوم حكينا انه ممكن تشوف خلايا مختلفة عن النورمال ولكن هذا لا يدل على انه الورم malignant**

By itself is not indication for malignancy

→ **A fibrous capsule (containing uniform tissue )** is often visible at the edge of the adenoma separating it from **compressed,** non-neoplastic parathyroid tissue. This constitutes a helpful internal control.

→ In contrast to the normal parathyroid parenchyma →

**adipose tissue is inconspicuous within the adenoma.**

**على عكس النورمال يلي بكون الانسجة الشحمية موجودة بصورة طبيعية هون بتصير غير واضحة وبتختفي**

**هاي الصفات مهمة وتذكرها منيح**

**(II) Parathyroid hyperplasia** (F8.7)

****By definition,** it is a **multiglandular process** with combined weight of all glands which may reach 1 gm.

عملية تشمل اكتر من غدة واحدة

حكينا انه وزنها الاصلي هو ثمن غرام يعني هون تضاعفت ٨ اضعاف حجمها الاصلي يعني اقل من A طبعا هاي بنوخدها وبنوزنها بميزان حساس جدا بعد ما نشيلها بالجراحة

**#◙ H,**

**(1)** the most common pattern is **chief-cell hyperplasia,** which may involve the glands in a diffuse or multinodular pattern.

اشهر نوع هو فرط نمو الخلايا من نوع **chief يكون على شكل شامل او عقد متعددة**

**(2)** Less commonly, the constituent cells contain abundant clear cytoplasm due to accumulation of glycogen **" water-clear cell hyperplasia"**.

As in A, **adipose tissue** is inconspicuous within foci of hyperplasia (same in A )

يعني برضه هون النسيج الشحمي ما رح يكون موجود

لانه فرط نمو ف رح يغطي على كل fats الموجودة داخله

ملاحظة على صورة 20-20 :

slight variation in nuclear size ( pleomorphism )

no anaplasia يعني مشابهة لخلايا الاصل

صورة 8.7 هاي لازم نعمل removal لكل ال all parathyroid يلي بالصورة لانه لوشلت ٣ و خليت وحدة رح تكبر وتستمر بالنمو

## (III) Parathyroid carcinoma

**Typically affect → **gland - single** usually it is firm or hard tumor, adhering to the surrounding tissue as a result of fibrosis (desmoplastic ) or infiltrative growth

**(at operation a → **a fibrous & adherent (fixed )** parathyroid is often a **clue** that the surgeon is dealing with a carcinoma rather than an adenoma!).

لما يسوي الجراح dissection ل post aspect of thyroid اذا شاف ورم او عقدة او كتلة **وكانت fibrous & adherent (fixed ) هون لازم تدير بالك لانه ممكن تكون ca ليش ؟ لانه فيه**

**A بينما ب adhesion / invasion to adjacent structures / fibrosis encapsulated / it is not invading بتكون**

**لذلك بتودي عينة مستعجلة للمختبر خلال ٢٠ د يبعتولك التشخيص حتى تعرف نوع العملية يلي رح تسويها ؟ هل رح تشيل ال A فقط وتطلع ولا اشي كله ال tumor مع other radial surgery**

**Parathyroid ca are larger than A , almost always → **more than 5 g & may exceeding 10g.**

**لما يصير وزنها ١٠ غرامات معناته كبرت ٨٠ ضعف حجمها الاصلي وبهاي الحالة ممكن المريض يحس فيها ولكن بصورة عاملة كل ال lesions تبعت ال parathyroid ما تيجي بسبب ال local mass effect ولكن تيجي بسبب لانه فيه hyperparathyroidism + hypercalcemia**

**#◙ H,**

*chief cells tend to predominate in most carcinomas.

*The cytologic features & mitotic activity can be quite variable, showing considerable overlap with those in A; therefore, neither can be reliably used to diagnose parathyroid ca.

overlap يتشاركوا ببعض الصفات عشان هيك ما بنقدر نحكم بالهستو اذا هاي A or ca لذلك نعتمد على شغلتين يلي تحت

**The only two valid criteria for malignancy are

**(1) Invasion of surrounding tissues (muscles ) &**

**غزو للانسجة المجاورة دليل انه الورم سرطاني**

**(2) Metastatic dissemination.**

****In primary hyperparathyroidism, the morphologic changes in other organs** deserving special mention are found mainly in the skeleton & kidneys

حكينا عن اشكال ال lesions تبعون **hyperparathyroidism بالغدة نفسها**
**يلي هما ca + A + hyperplasia طب شو رح تعمل ب other organs**

**# Skeletal changes**:

**include prominence of osteoclasts, which in turn **erode bone matrix** & mobilize calcium salts.

PTH يشجع ال osteoclasts انها توكل العظم بالكامل وتطلع الكالسيوم للدم فيزيد بالدم

بالتالي اذا زاد ال PTH رح يصير يلي عليه خط رح يصبح ممتص العظم بسبب هضمه من قبل ال osteoclasts ويصبح العظم ضعيف

→ **Bone resorption** →is accompanied by ↑ **osteoblastic**

activity & the formation of new bone trabeculae.

حتى يعوض عن العظم الذي تم امتصاصه

**The resultant bone contains widely spaced, delicate trabeculae similar to those seen in **osteoporosis** **(common affect females more than males ) .**

**بالنتيجة العظم الذي تكون جديد رح يكون ضعيف وفي فراغات ورقيق**

****In more severe cases, the cortex is grossly thinned, the marrow contains cysts with ↑ amounts of fibrous tissue accompanied by foci of hemorrhage (osteitis fibrosa cystica, F13-42).**

**cortex is grossly thinned** بالتالي قابل للكسر بالاضافة للاكياس جوا نخاع العظم تحتوي على fibrous tissue

**osteitis** : misnamed …. Because it is definitely not inflammation

**Aggregates of osteoclasts, reactive giant cells, & hemorrhagic debris occasionally form masses that may be mistaken for neoplasms → (**Brown tumors of hyperparathyroidism**).

بس تنظر بال x ray تبين انها tumor ولكنه بالحقيقة ليس ورم هو مجرد انه الخلايا يلي عليها خط تجمعت وسوت هاد المنظر

يلي بالبولد هو مجرد عنوان وبرضه تسمية خاطئة لانه مو tumor

**# Renal changes:**

**الاخطر**

PTH-induced hypercalcemia favors the

(1) formation of urinary tract stones → **(nephrolithiasis)**

حصى بالمجاري البولية تتكون لانه ca secreted in urine بكميات كبيرة

بانجلترا اول ما حد يلاقوا معه حصى بخلوا يعمل فحص ال PTH لانه هناك ال genetic factors +dehydration نادر

(2) calcification of the renal interstitium & tubules →

**(nephrocalcinosis).**

**تكلسات الكلوية**

**# Metastatic calcification secondary to hypercalcemia** may also be seen in other sites, including the stomach, lungs, myocardium, & blood vessels

عنا اشي اسمه dystrophic calcification هاد تجمع الكالسيوم بالاماكن الميتة زي caseating TB or infarction ولكن هون الانسجة طبيعية بس لانه مستوى الكالسيوم عالي في الدم كتير

***#Clinical Features***

**Primary hyperparathyroidism** is:

• Usually a disease of **adults** & is **more common in women** than in men by a ratio of **3:1.**

• It' most common manifestation is ↑ serum ionized calcium.

اهم

• It is the most common cause of ***clinically silent hypercalcemia.***

But many other conditions produce hypercalcemia (Table 20-4).

***Malignancy,*** in particular, is the most common cause of ***clinically apparent hypercalcemia*** in adults, and it usually

associated with poor prognosis, as it is more frequently occurs in individuals with advanced cancers.

☼ (I) In persons with hypercalcemia caused by **parathyroid hyperfunction,** → serum **PTH** is inappropriately **elevated**, (II) whereas serum **PTH is low to undetectable** in hypercalcemia caused by **nonparathyroid diseases**, including malignancy.

ê PTH excess causes hypercalcemia, hypophosphatemia & ↑ urinary excretion of both calcium & phosphate

(Table 20-4 Causes of hypercalcemia

**(I) Raised PTH:** Hyperparathyroidism: ***Primary** (adenoma > hyperplasia, the most common cause of hyper-calcemia overall), Secondary ☨, Tertiary, ☨

Familial hypocalciuric hypercalcemia.

**(II) Decreased PTH** Hypercalcemia of ***malignancy** (most common cause of *symptomatic* hypercalcemia), Osteolytic metastases, PTH-related protein mediated, Vitamin D toxicity, Immobilization, Drugs (thiazide diuretics), Granulomatous diseases (sarcoidosis).

*(Primary hyperparathyroidism & malignancy account for nearly **90%** of cases of hypercalcemia).

**Secondary Hyperparathyroidism**

Secondary hyperparathyroidism is caused by any condition associated with a **chronic** depression in the serum calcium level **(hypocalcemia),** leading to compensatory over activity of the parathyroids. ***Renal failure is by far the most common*** *cause of secondary hyperparathyroidism.*

The **mechanisms** failure induces
secondary hyperparathyroidism are complex & not fully understood. Chronic renal insufficiency is associated with

→ ↓ phosphate excretion, resulting in

→ hyperphosphatemia, the elevated serum phosphate levels

→ directly depress serum calcium levels & thereby

→ stimulate parathyroid gland activity.

▼ In addition, loss of renal substances reduces the availability of $\alpha$ 1-hydroxylase necessary for the synthesis of the active form of vitamin D, which in turn reduces intestinal absorption of calcium.

**GROSSLY, all** the parathyroid glands in secondary hyperparathyroidism are **hyperplastic.**

◙ **H,** the hyperplastic glands contain an ↑ **number of chief cells,** or **wate**r-**clear cells,** in a diffuse or multinodular distribution. Fat cells are decreased in number.

**Bone abnormalities** ***(renal osteodystrophy)*** similar to

those seen in primary hyperparathyroidism may also be present. **Metastatic calcification** may be seen in many tissues, including lungs heart, stomach, & blood vessels L*Tertiary hyperparathyroidism*: In a minority of patients, parathyroid activity may become autonomous & excessive, with resultant hypercalcemia; a process sometimes termed *tertiary hyperparathyroidism.* Parathyroidectomy may be necessary to control the hyperparathyroidism in these cases.

**HYPOPARATHYROIDISM**

Is far *less common* than is hyperparathyroidism!!! **Causes are:**

***Surgical*** removal of parathyroids during thyroidectomy.

***Congenital absence****:* usually occurs in conjunction with thymic aplasia & cardiac defects in **DiGeorge syndrome**.

***Autoimmune hypoparathyroidism****:* a hereditary polyglandular deficiency syndrome arising from auto-Abs to multiple endocrine organs (thyroid, parathyroid, pancreas, & adrenals).

***# The*** **major clinical manifestations of hypoparathyroidism are** referable to hypocalcemia & include:

↑ ***neuromuscular irritability*** *(tingling, muscle spasms, facial grimacing, & sustained carpopedal spasm* ***or tetany****),* **cardiac arrhythmias** & on occasion,

↑ *intracranial pressures* & *seizures*