GO OVER ENDOCRINE EMERGENCY

LOI clinical Physio of PTH & Ca^{2+}/PO_4 metab

CALCIUM

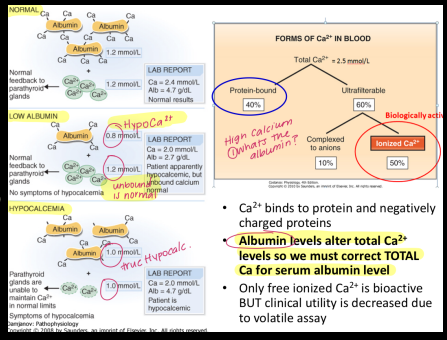
★ Albumin levels alter total Ca^{2+} levels → correct total Ca^{2+} for serum albumin

1g ΔAlb = 0.8mg ΔCa²⁺

TQ [corrected Ca^{2+} = Measured Ca^{2+} + 0.8(4 - Serum Albumin)]

→ hypocalcemia w/ low albumin may be normal ★★

★ only ionized (free) Ca^{2+} is biologically active



- Ca^{2+} binds to protein and negatively charged proteins
- **Albumin levels alter total Ca^{2+} levels so we must correct TOTAL Ca for serum albumin level**
- Only free ionized Ca^{2+} is bioactive BUT clinical utility is decreased due to volatile assay

★ Acid/Base disturbances:

→ Acidemia = ↑free Ca^{2+}

→ Alkalosis = ↓free Ca^{2+}

] false levels → This is why total Ca^{2+} is more reliable than ionized

★ Ionized Ca^{2+} variation:

TQ ★ Hypocalcemia = ↑membrane excitability & PROLONGED QT ★ + spasm, ⊕ chvostek sign, seizures

– caused by Hypoparathyroid, renal dz, malabsorption, vit. D def.

★ Hypercalcemia = ↓membrane excitability & SHORT QT + stones, groans, bones, psych overtones

– 1° or 3° HyperPTH, MEN, MALIGNANCY ★

PARATHYROID HORMONE released by chief cells of parathyroid; increases in response to low Ca^{2+}, high PO_4, low Mg^{2+}

TQ ★★ if Ca^{2+} is HIGH & PTH is LOW → MALIGNANCY "malignant hypercalcemia"

[tumor secretes PTHrP]

★ PTH acts on osteoblasts, which activate RANK on osteoclasts

= Bone breakdown/resorption

also: phosphaturia @ PCT
calcium resorption @ DCT
] @ kidney

Ø direct effect on intestine

→ stimulates 1α-hydroxylase in kidney, which makes vit. D, which upregulates Ca^{2+} gut reabsorption

Hypercalcemia of malignancy

- Most common cause of hypercalcemia in the inpatient setting
- Can be from bone metastisis
- Malignant tumors can also secrete PTH-related peptide (PTH-rP) → acts on PTH-R
  - Hypercalcemia — sits on PTH receptor; acts like it
  - Hypophosphatemia
  - colon, prostate CA
- Treated with:
  - Furosemide → increases Ca2+ excretion in the urine — pee out Ca^{2+}
  - IV hydration
  - Bisphosphonate → bone resorption inhibitor (stops Ca from coming out of bone)

★ HYPERPARATHYROIDISM

Primary: caused by benign ↑PTH secreting tumor = Parathyroid Adenoma ★

causes hypercalcemia from bone resorption → SLOW, short QT

- if they have systemic effects → surgery

BUZZ: salt & pepper skull / radiographs showing damaged bone

★ can have kidney stones w/ hyper and hypo PTH

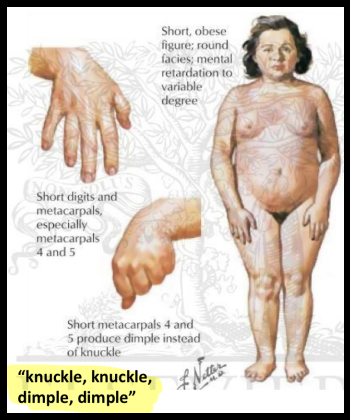
Secondary: HyperPTH in response to chronically ↓Ca^{2+}

vit. D def / renal dz

Tertiary: after kidney transplant, calcium normalized but PTH stays high

TQ ★ HYPOPARATHYROID → causes hypocalcemia

★ Pseudohypoparathyroidism: ↑PTH, defective PTH receptor ★



"knuckle, knuckle, dimple, dimple"

LO2 Path of Parathyroid glands & MEN

PTH = ↑cAMP (Gs) → binds osteoblasts to ↑RANK

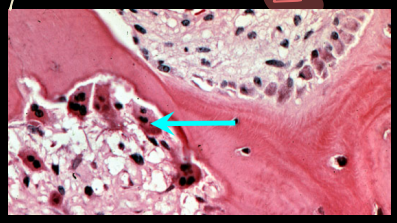
Primary HyperPTH: MC Parathyroid adenoma ★ ↑Ca^{2+}, ↑PTH

→ px: Bones, stones, groans, psych overtones

★ Osteoporosis: ↑bone porosity, ↓bone mass → vertebral compression fx

★ Osteitis fibrosa cystica: overactivity of osteoclasts = large LYTIC LESION looks like multiple myeloma
- hemorrhagic / brown tumor
- numerous giant cells & ingrowth of vascularized fibrous tissue & OSTEOCLASTS
- 1st sign = well demarcated, radiolucent tumor-looking spaces
- ↑Alk Phos, high urine Ca^{2+}

TQ lytic lesions, histo shows osteoclasts, hx long standing hyperPTH & ↑Alk Phos



Secondary HyperPTH MC CKD ↓Ca^{2+}, ↑PTH

TQ pathophys Renal Dz = retention of PO_4 → increase FGF23, decrease vit. D, dec. Ca^{2+}, ↑PTH
→ parathyroid hyperplasia

↑FGF23 = CKD

★ Hypercalcemia w/o elevated PTH is most commonly caused by malignancy

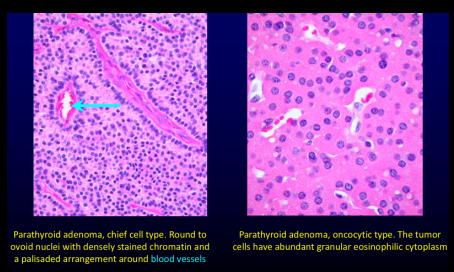
Parathyroid Adenoma: solitary lesion composed of chief cells, remaining glands shrunken

TQ parathyroid adenoma = cyclin D overexpression ★ MEN1 mutation RET or CaSR mutation

MC mutation in MEN1 gene (11q13)

dx: sestamibi scan (100% specificity) — wont show hyperplasia

histo: rim of normal PT tissue



Parathyroid adenoma, chief cell type. Round to ovoid nuclei with densely stained chromatin and a palisaded arrangement around blood vessels

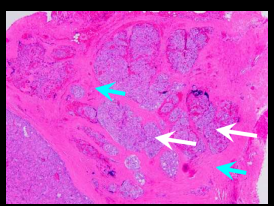
Parathyroid adenoma, oncocytic type. The tumor cells have abundant granular eosinophilic cytoplasm

Parathyroid carcinoma

px: vocal cord paralysis

dx: based on evidence of INVASION

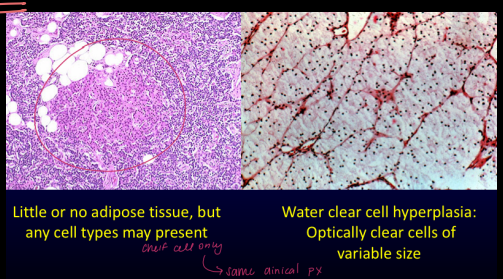
histo: large & irregular, dense fibrous bands; invading



Primary Chief Cell Hyperplasia ↑PTH; MEN1 & 2A

involves all glands

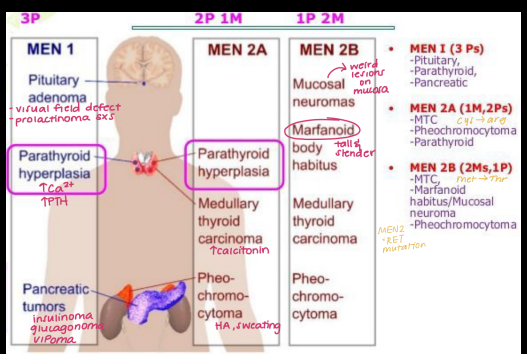
★ No rim of normal tissue identifiable



Little or no adipose tissue, but any cell types may present — chief cell only → same clinical px

Water clear cell hyperplasia: Optically clear cells of variable size

HY



★ **Autosomal Dominant HypoPTH**: GoF CASR gene
hypocalcemia w/ hypercalciuria & normal/low PTH

MEN benign or malignant tumors involving at least 2 endocrine organs ★★

TQ

MEN1: MC parathyroid, pituitary, & enteropancreatic tumors
auto dominant MEN1 mutation

MEN2: thyroid medullary carcinoma & pheochromocytoma
RET mutation = RTK ; gain of function mutation

LO3 Metabolic Bone Dz

- Understand relationship of bone structure/function to disorders of bone ✓
- Recognize primary osteoporosis ✓
- Discuss secondary causes of osteoporosis ✓
- Describe causes of osteomalacia and rickets ✓ vit. D deficiency caused by…
- Understand diagnosis and treatment of osteomalacia ✓
- Diagnosis of Paget's disease of bone

★ Bone structure & function:
- rigid support, f(x) as a lever
- ionic reservoir for Ca, PO_4, Mg, Na] required for hyalinization
★ Cortical Bone: long bones, densely packed
★ Trabecular bone: cancellous, axial spine
= elasticity & strength
defect = vertebral fx

★ Bone Remodeling does NOT require hormones, it is just altered by them
→ only requires vit. D
Hormonal effects:
Activation of remodeling: Hyperthyroid, HyperPTH, hypervit. D

TQ pt px w/ osteoporosis, what could they have done to prevent it?
A physical activity/ weight-bearing exercise in mid 20s - early 30s

OSTEOPOROSIS low bone mass, prone to fragility fractures → affects trabecular bone = vertebral compression fractures ★★ T10-L2 TQ A

★ Primary: age related, menopause

★ Secondary: caused by specific disorder
- Hyperthyroid ↑ bone resorption by T_3/T_4 stimulating osteoclasts directly
(pts w/ ↓TSH = increased risk)
- Glucocorticoid excess = dose dependent
  - ↓Ca^{2+} absorbed in gut
  - ↑osteoclasts
  - ↓IGF-1
- Hypogonadism
  - androgens stimulate osteoblasts directly
    - give testosterone + weight bearing
    - if prostate CA - give teriparitide
- FEMALE ATHLETE TRIAD
  1. malnutrition
  2. amenorrhea
  3. osteoporosis

↓leptin disrupts HPO axis = ↓estrogen = ↓peak bone mass
tx: weight gain

TQ ★ Female Athlete Triad tx: weight gain, proper nutrition, vitamin D, & weight-bearing exercise

Table 8–9 Causes of Secondary Osteoporosis.

Endocrinopathies	★ Hypogonadism = ↓Estrogen
Thyrotoxicosis	
Hyperprolactinemia	
Primary hyperparathyroidism	
Acromegaly	
Hypogonadism	
★ Glucocorticoid excess	– Cushings
Gastrointestinal/nutritional	
Vitamin D deficiency	★ → malabsorptive or from environmental deficiency
Chronic liver disease	
Celiac sprue	
Malabsorption	
Medications	
Glucocorticoids	→ pt w/ lupus, Chron's
Androgen deprivation therapy with gonadotropin-releasing hormone agonists	
Certain anticonvulsants	
Excess thyroid hormone replacement	long term depo medroxyprogesterone birth control shot
Other	
Alcoholism	– young patients!
Osteogenesis imperfecta	
Rheumatoid arthritis	→ double whammy w/ destruction and steroid use
Multiple myeloma	
Chronic obstructive pulmonary disease	
Idiopathic hypercalciuria	

VITAMIN D DEFICIENCY

★ Osteomalacia: decreased mineralization of newly formed bone @ sites of turnover = SOFT BONE ★ closed epiphyseal plate

sxs: skeletal pain & weakness that gets WORSE w/ activity, esp @ hip girdle

TQ dx: [↑PTH, ↓calciuria, ↑Alkphos, ↓vit. D] ★★

tx: vitamin D, get sun W/O sunscreen (15min/day)
tx underlying cause → renal issues (nephrotic syndrome) or phosphate disorders

★ Rickets: Nutritional vit. D deficiency → baby on soy milk needs fortification

TQ ★ High prevalence in dark skinned, breastfed babies in cold climates ★
px: skeletal pain & deformity → soft long bones = BOWING + pot-belly, waddling gait, poor dentition
tx: vit. D supplement high dose

★ Diagnosis of Paget's Dz: osteolytic → MIXED → sclerotic → quiescent

path: large osteoclasts + WOVEN BONE
in sacrum, spine, femur, skull

labs: ↑AlkPhos!! calcium usually normal

Paget's disease of bone

- Can effect most body systems
  - Neurologic
    - deafness, nerve compression → small bones of ear/skull
  - Rheumatologic
    - Fracture risk
    - Joint replacements due to early arthritis
  - Neoplastic
    - Osteosarcoma – rare, less than 1%
  - Metabolic – high output heart failure
- Treatment?
  - Treat pain – NSAIDS
  - Bisphosphonates
    - Stop bone resorption at the osteoclast
  - Calcitonin
    - If can't tolerate bisphosphonates

not a simple lab to treat it

- Hypercalcemia of Malignancy
  - Understand WHY it happens ✓
  - Know the most common malignancies associated with hypercalcemia – both solid and hematologic ✓
- Ectopic Cushing's Syndrome
  - Understand what differentiates between Cushing's Syndrome, and ectopic Cushing's syndrome ✓
  - Know what tumors cause ectopic ACTH ✓
  - Explain initial diagnostic workup for those malignancies ✓

LO4 MEN & Neoplasia:

TQ **HYPERCALCEMIA of MALIGNANCY**: tumor secretes PTHrP which acts on PTH receptor to breakdown bone
∴ ↑calcium, ↓PTH, ↓vit. D ★

- solid → Renal cell carcinoma, squamous cell carcinoma (lung) & Breast carcinoma
- heme → Adult T-cell Leukemia

tx: bisphosphonates & glucocorticoids (palliative)

Function of PTHrP ★ = ↑Hypercalcemia

- Produced by local tumor (bone mets) or systemic effect
- Stimulates RANKL expression (Receptor Activation of Nf-KB ligand), which modulates bone resorption by stimulating osteoclast differentiation — tx: bisphosphonates
  (RANKL stimulates osteoclasts)
- In contrast to normal PTH, calcium levels do not modulate its production
- In contrast to primary hyperparathyroidism: 1, 25 (OH)2 vit D is normal or suppressed and the effects are more substantial (in 1° hyperPTH, vit. D increases)
- Also – with PTHrP from bone mets, IL-1 alpha and IL-6 inflammatory mediators contribute to increased bone resorption ↑ stim. osteoclast

ECTOPIC CUSHINGS SYNDROME Ø typical signs of hypercortisolism

px: HTN, diabetes, weight gain, hyperpigmentation

RAPID ONSET ★, ↓CRH, ↑ACTH, ↑cortisol, Ø suppression w/ dexameth.

TQ tumors: carcinoid, neuroendocrine, & SMALL CELL LUNG CA ★★

dx: CHEST XRAY "pt px w/ patchy tan & abrupt onset HTN" → get CXR

- Objectives
  - Inheritance patterns and genes responsible for MEN 1 and MEN 2a and MEN 2b ✓
  - Distinguish common features of all three syndromes
  - Understand screening and follow-up of genetically predisposed populations ✓

MEN autosomal dominant!

MEN1 = MEN1 mutation on 11q13

→ parathyroid, enteropancreatic, & pituitary tumors

★ screen anyone w/ Zollinger-Ellison (gastrinoma)

if ⊕genes: screening
1. fasting gastrin, Ca, & alb
2. MRI pituitary every 3yr
3. anterior mediastinal /abdomen CTs

tx: remove parathyroids, PPI for gastrinoma

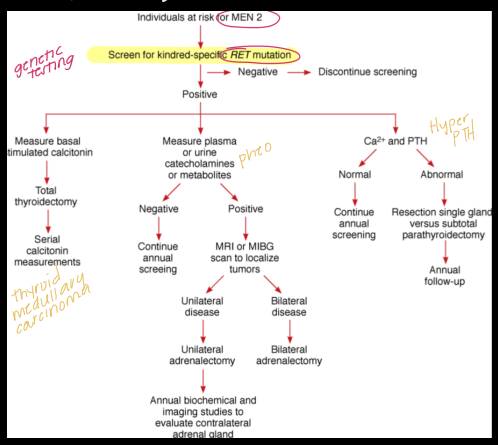
MEN2a/2B RET mutation
- 2a: cysteine → arginine
- 2b: methionine → threonine

→ pheochromocytoma & thyroid medullary carcinoma (+ mucosal neuromas in 2b)

2b also associated w/ Marfanoid body habitus

screening: ⊕RET → check calcitonin, catecholamines, Ca^{2+} & PTH

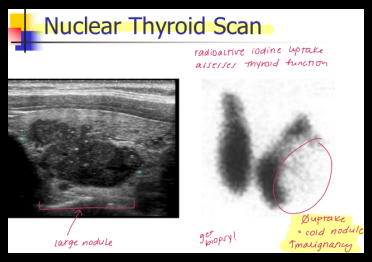
tx: thyroidectomy ASAP
tx pheos w/ α/β blocker then resect



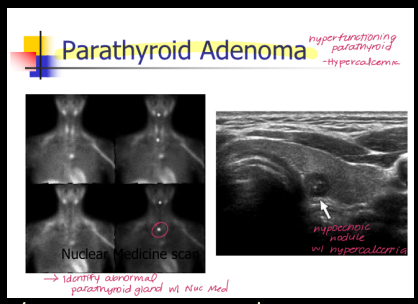
LOL Endocrine Radiology

- Pituitary: [MRI w/ & w/o contrast] TQ MRI of sella turcica!
  "pt complains of double vision" or "bilateral milky breast discharge"

- Thyroid: high frequency ultrasound (w/ vascular flow maybe)
  "pt px w/ fatigue, WL, palpitations, difficulty swallowing, & palpable thyroid"
  * Nodule = hypoechoic
  * Goiter = heterogenous appearance
  → Nuc Med scan
  Ø uptake = cold nodule = ↑malignancy (get biopsy)



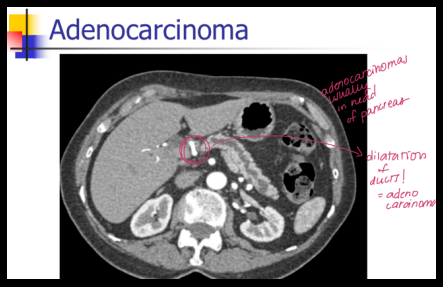
- Parathyroid: ultrasound & Nuc Med
  pt px w/ sxs of hypercalcemia



- Adrenal Gland: CT of abdomen & pelvis w/ & w/o
  pt px w/ hormonal imbalances or metastatic dz ← hx of lung cancer
  → Pathology presents:
  1. Hyperplasia → Cushing's (px HTN & ↑HbA1C) & Adrenogenital syndrome (congenital)
  2. Hyperfunctioning adenoma → Conn's syndrome (hyperaldosteronism)
  3. adrenocortical carcinoma

  * Pheochromocytoma: catecholamine secreting tumor from chromaffin cells of SNS
  pt px w/ episodic HTN, palpitations, SOB, sweating, HA
  TQ → get abdominal and pelvic CT
  → 2nd location = organ of Zuckerkandl

- Pancreas: CT
  * Acute Pancreatitis: wispy on CT, ill defined
  → gallstones & alcoholism
  * Chronic Pancreatitis: calcifications on CT & atrophic w/ ductal dilation
  → alcoholism & familial hyperlipidemia
  - exocrine dysfunction!
  * Pancreatic Tumors:
  → islet cell tumors
  endocrine dysfunction! → Enhance brightly on CT
  insulinoma, gastrinoma, glucagonoma
  → Adenocarcinoma
  dilation of pancreatic duct (bright)



L07 Endocrine surgery → Thyroid

THYROID

Benign conditions:

★ Thyroglossal Duct cyst:
- congenital midline painless mass

TQ → Sistrunk procedure:
must remove part of hyoid & dissect up to base of tongue

★ Nontoxic Goiter:
- incidental or px w/ compression sxs

→ total thyroidectomy

★ Toxic Goiter:
- ↑thyroid hormone, ↓TSH, must r/o autoimmune dz

→ thionamide medications (make euthyroid before surgery
↓
surgery (I131 for pts who aren't good candidate)

★ Toxic Adenoma: hyperfunctioning nodules
- ↑thyroid hormone, ↓TSH → thyrotoxicosis

→ radioactive iodine or lobectomy

THYROID CANCER
rapid growth, pain, hoarseness, stridor, hemoptysis

RF: radiation! - acne tx, hx cancer

Evaluation: nodules w/ ↑TSH & cold nodules → FNA
nodules ≤1cm w/ suspicious or ≥1.5cm

FNA Results: ideal = Bethesda 2 (all thyroid cells look normal)

TQ ★What Bethesda classification has the lowest risk of malignancy?
A: Class 2

★ Papillary carcinoma: MC well differentiated, majority radiation induced
- histo: orphan annie eyes & psammoma bodies
- tx: total thyroidectomy

TQ → [OR lobectomy w/ isthmusectomy
if <45 y/o, Ø radiation, Ø LN involvement, Ø distant mets, <4cm]

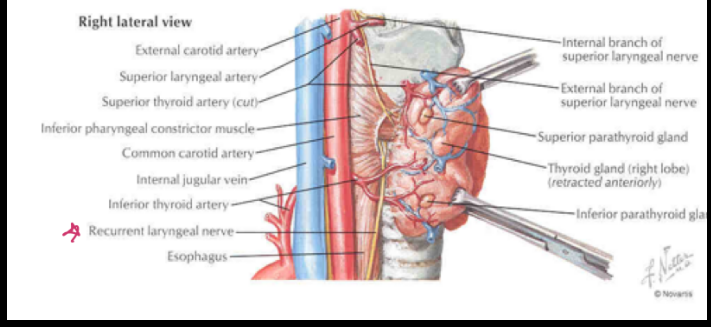
★ Follicular carcinoma: female 50yo, iodine deficiency
- distant mets d/t hematogenous spread
- dx: lobectomy
- tx: total thyroidectomy if invasive ± LN neck dissection

★ Hurthle Cell Carcinoma: most aggressive WDTC
- dx: lobectomy
- tx: total thyroidectomy if invasive ± LN neck dissection

★ Medullary Carcinoma: Calcitonin producing tumor! Sporadic or familial (MEN2) = BAD
- tx: adequate pre-op assessment for pheo
total thyroidectomy w/ central node dissection
± ipsilateral neck dissection, contralateral if nodes are ⊕

★ Anaplastic Carcinoma: most aggressive, worst prognosis
- unencapsulated, expands out of neck
- tx: palliative debulking

Surgery complications:



Preferred Thyroid Procedures

- Lobectomy → determine if cancerous
  - Complete removal of one lobe and isthmus
- Near Total Thyroidectomy tx CA, or goiter
  - Complete removal of one lobe and isthmus and all but 1cm of contralateral lobe — only done if you're worried about laryngeal
- Total thyroidectomy ★HY
  - Complete removal of both thyroid lobes, isthmus, pyramidal lobe

Thyroid Cancer

- Risk factors - Radiation ★low or high dose
  - low or high dose external irradiation
  - especially in childhood for:
    - large thymus, acne, enlarged tonsils, cervical adenitis, sinusitis, and malignancies
  - 5% of pts with history of low-dose radiation exposure develop a thyroid malignancy
  - Solitary nodule and history of radiation exposure
    - 40% of these nodules will harbor carcinoma
    - ★ pts who worked in Radiology ★ 1 hr Oak Ridge??

PTs who are old

Thyroid Nodule FNA Results

- Bethesda Classification
  - 1 Ø enough thyroid cells to make dx
    - Repeat
  - 2 - what we want → all thyroid cells look normal risk malig (3-4%)
    - US in one year
  - 3 & 4 (Gray Zone) indeterminate
    - Gene Expression Classification
      - Afirma★ → 15% risk; if ⊕ = 50% if ⊖ = 3-4%
      - Thyroseq
  - 5 & 6 ← Dx of CA
    - Surgery

suspicious of CA

TQ
* Recurrent Laryngeal Nerve injury → bilateral vs unilateral (airway obstruction / hoarseness)
* Superior Laryngeal Nerve injury → ↓pitch
* Parathyroid gland removal → HYPOCALCEMIA
* Bleeding & airway obstruction

LOB Endocrine surgery II

PARATHYROID

TQ
- blood supply: inferior thyroid aa.
- superior gland: posterior & lateral to recurrent laryngeal
- inferior gland: anterior & medial to recurrent laryngeal

surgical indications: Hyperparathyroidism w/ Hypercalcemia sxs

OPERATIONS:
* adenoma → MIRP or 4 gland exploration
* hyperplasia → subtotal/total parathyroidectomy w/ allograft

complications: hypo/hypercalcemia, Recurrent laryngeal N.

* paratnyroid carcinoma: heterogenous, dx confirmed @ surgical resection

ADRENALS

vasculature: left adrenal vein → left renal vein
right adrenal vein → IVC directly
TQ

- surgical indications: functional tumors & tumors > 4cm

* PHEOCHROMOCYTOMA: tx = surgery BUT medically optimize PRIOR
TQ
① Phenoxybenzamine (α antagonist) 1-3 wks prior
- can give β blocker AFTER α blockade if uncontrolled tachycardia
→ (stroke/MI if before)

pretreat pheos w/ phenoxybenzamine prior to surgery

- if you find incidentaloma
→ work up to make sure its nonfunctional
- catecholamines, potassium/aldo, cortisol & metanephrines
- rule out other malignancy
→ observation if <4cm, nonfunctioning
TQ
* ØCT guided biopsy on adrenals!

* * always remove if functioning tumor

PANCREAS

Endocrine pancreas: always evaluate for MEN!

MEN!
① insulinoma = MC islet cell tumor
- whipples triad
tx: enucleation surgery

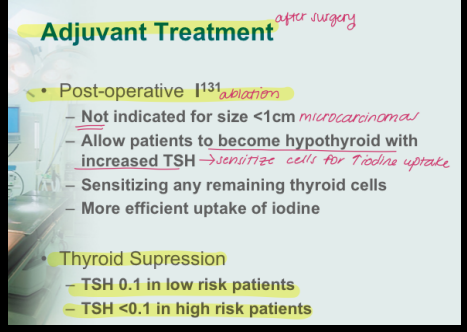
② glucagonoma = malignant
- diabetes, DVT, dermatitis, diarrhea, declining weight

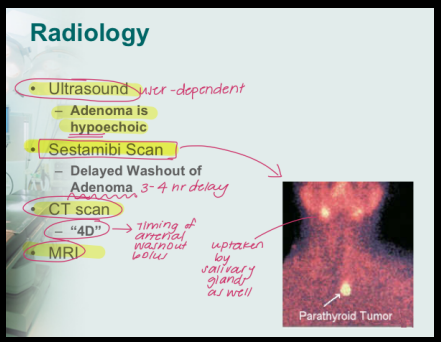
③ VIPoma = diarrhea
>5L/day
cramps!

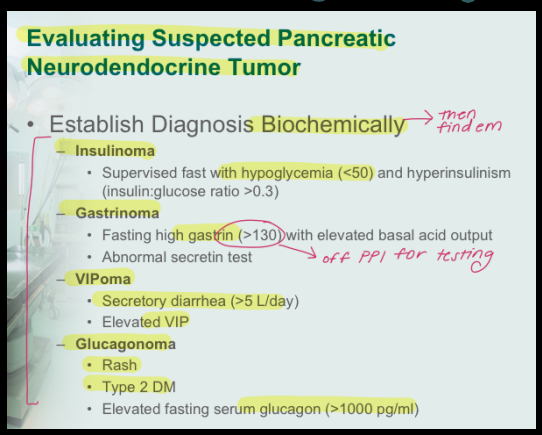
④ Gastrinoma = Zollinger Ellison
tx
- Whipple
- Enucleation
- distal pancreatectomy

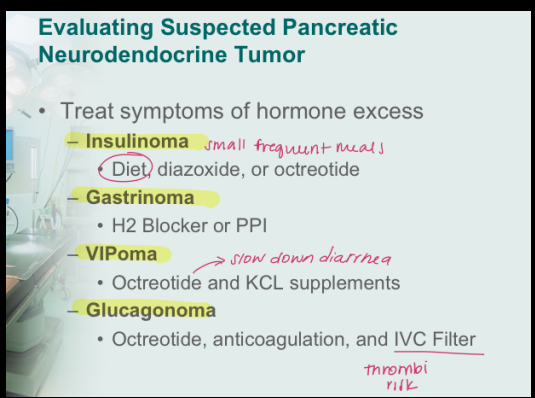
⑤ Somatostatinoma
- Gallstones! Diarrhea! Steatorrhea!

MC complication after pancreatitis
= pseudocyst*









WANG PQs:

PARATHYROID

- ✓ 1. C — Hypercalcemia (Hyper PTH) ↑Ca^{2+} ↓Phos ↑AlkPhos
- ✓ 2. B — hx of invasive ductal carcinoma → PTHrP
- ✓ 3. E — lytic bone lesions @ hands & mandible → get intact PTH
- ✓ 4. D — ↑PTH ⊕ sestamibi scan = Adenoma!
- ✓ 5. D
- ✓ 6. D — ↑Ca ↑PTH 2 enlarged PT glands ⊖ sestamibi = Hyperplasia
- ✓ 7. D * — ↑Ca & subperiosteal absorption in hands
- ✓ 8. A — muscle cramps & hx diabetic nephrop. = CKD
- 9. ~~D~~ E — ↓Ca ↑Phos ↑PTH = 2° HyperPTH caused by chronic ↓Ca^{2+} due to retention of Phosphorus (WHY?)
- ✓ 10. D
- ✓ 11. E * — Hypercalcemia & CKD ; ↑Ca, ↑Phos, ↑BUN & Cr ↑↑PTH → CKD tx w/ dialysis = 3°?
- ✓ 12. C — DM, HTN, obesity, depression ; ↑Ca, ↓PO_4, ↑↑PTH
- ✓ 13. A — ↓Ca, ↑Phos ↓PTH
- ✓ 14. C — 3 yo ↓Ca ↑PTH = Pseudohypoparathyroid
- ✓ 15. A — hx pituitary = MEN1 ; ↑Ca^{2+} ; ulcers = Zollinger Ellison ; ↑PTH & ↑gastrin
- ✓ 16. B
- ✓ 17. A
- ✓ 18. B — thyroid mass, hx parathyroid hyperplasia
- ✓ 19. E — "salt & pepper chromatin" & amyloid deposition = Medullary carcinoma
- ✓ 20. C