Stones Groans Moans

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Disclosures

- Consultant Medtronics
- Advisory Board Ascendis
- Speakers Bureau Veracyte

Learning Objectives

- 1. Review the updated recommendations from 2022 International Taskforce for the management of primary hyperparathyroidism
- 2. Discuss current treatments and post op complications
- 3. Discuss the pros and cons of preoperative imaging and its value to surgical intervention
- 4. Discuss better understanding of Normocalcemic Hyperparathyroidism
- 5. Discuss hypoparathyroidism briefly

Brief History

- ~1850 Sir Richard Owen, Royal College of Surgeons of England describes parathyroid glands Indian Rhinoceros
- 1880 Ivar Sansdström, Swedish medical student University of Uppsala identified the glands in humans
- 1891 von Recklinghausen reported on a pt who had multiple atraumatic fractures, long bone 'bending' and fibrosis, brown tumors and cysts—*osteitis fibrosa cystica of von Reckinghausen*
- 1925 in Vienna, Felix Mandl first parathyroidectomy

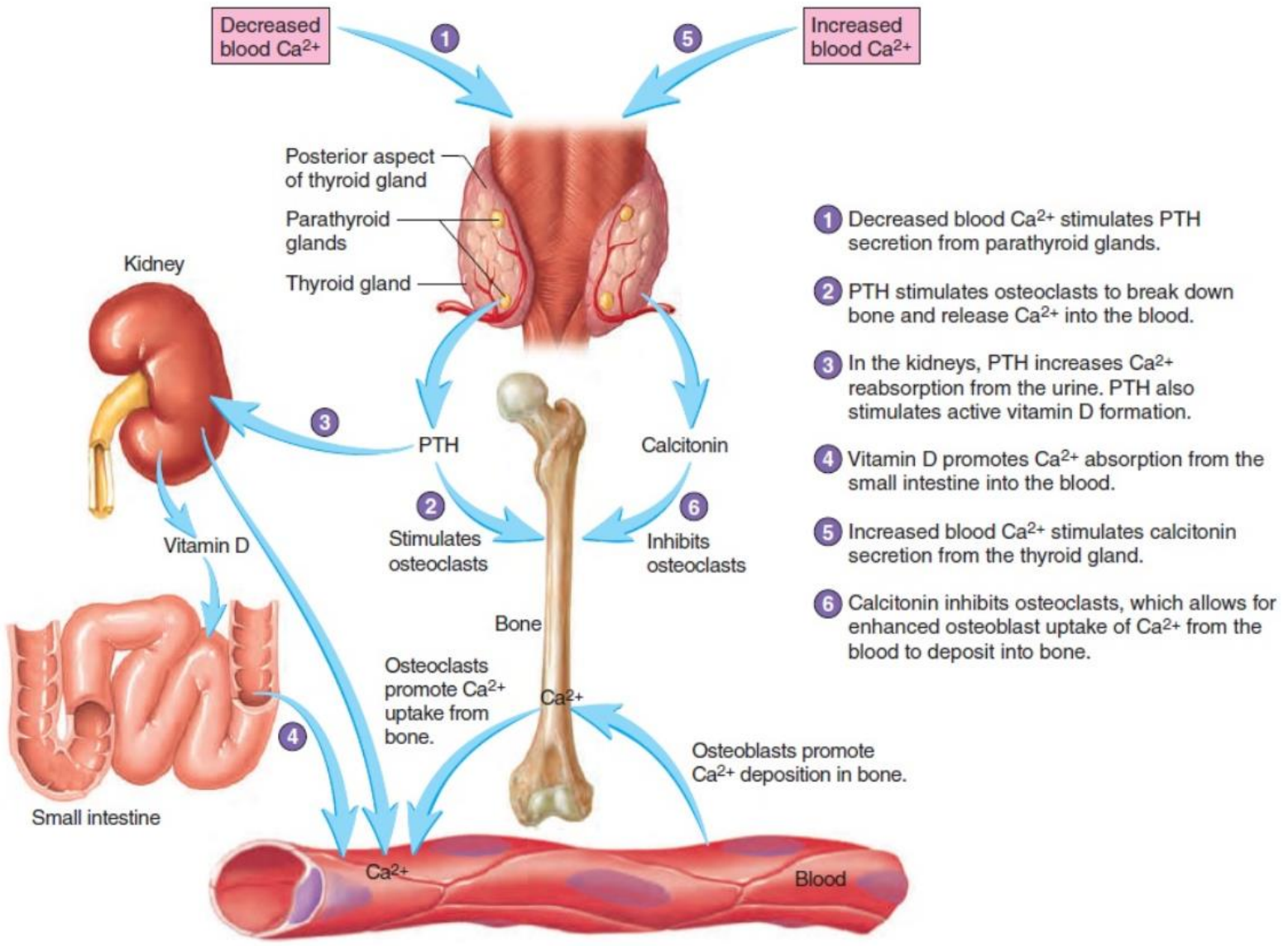
Captain Charles Martel

- 1926 Martel admitted to NYC metabolism clinic; referred to MGH
- First person dx'd in US
- 9th surgery tumor in chest cured his disease
- 1977 Noble Prize for PTH assay
- 1991 Dr Irvin PTH mediated surgery
- Today: Surgical use of autofluorescence

Current guidelines

- Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop **2022** Bilezikian JBMR

- The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism **2016** Wilhelm JAMA Surgery


Decreased blood Ca^{2+}
Increased blood Ca^{2+}
Posterior aspect of thyroid gland
Parathyroid glands
Thyroid gland
Kidney
PTH
Calcitonin
Vitamin D
Stimulates osteoclasts
Inhibits osteoclasts
Bone
Osteoclasts promote Ca^{2+} uptake from bone.
Ca^{2+}
Osteoblasts promote Ca^{2+} deposition in bone.
Small intestine
Ca^{2+}
Blood
1 Decreased blood Ca^{2+} stimulates PTH secretion from parathyroid glands.
2 PTH stimulates osteoclasts to break down bone and release Ca^{2+} into the blood.
3 In the kidneys, PTH increases Ca^{2+} reabsorption from the urine. PTH also stimulates active vitamin D formation.
4 Vitamin D promotes Ca^{2+} absorption from the small intestine into the blood.
5 Increased blood Ca^{2+} stimulates calcitonin secretion from the thyroid gland.
6 Calcitonin inhibits osteoclasts, which allows for enhanced osteoblast uptake of Ca^{2+} from the blood to deposit into bone.

Primary Hyperparathyroidism

Classic Primary Hyperparathyroidism	**Asymptomatic** Hyperparathyroidism	**Normocalcemic** Hyperparathyroidism
• Rare in the US • Marked hypercalcemia • Osteitis fibrosa cystica • Nephrolithiasis, nephrocalcinosis, CKD • Polyuria and polydipsia	• Often incidental on labs • **Elevated calcium** • **High or inappropriately normal PTH** • May not truly be "asymptomatic"	• Often detected during osteoporosis evaluation • **Normal calcium & iCa** • **Elevated PTH** • Secondary HPT must be excluded

Recommended work-up for PHPT

- [ ] Calcium, albumin, PTH, phos, Alk phos, creatinine, 25 OH vit D
- [ ] 24 hr urine calcium and creatinine
- [ ] Stone risk profile (**If UCa >250 mg/d women, >300 mg/d men**)
- [ ] 3-site DXA (including 1/3 radius)
- [ ] Vertebral spine assessment (radiography, VFA)
- [ ] Abd imaging (radiography, US, *CT*)

Optional work-up

- [ ] Genetic testing if genetic cause suspected (young age, multigland, PT carcinoma, syndromic features)
- [ ] HRpQCT (Not *recommended* b/c of lack of availability)
- [ ] TBS by DXA (uncertain utility)
- [ ] Bone turnover markers

Differentiating Primary HPT from FHH

Disorder	Serum Calcium	PTH	Phosphate	Urine calcium excretion
Primary HPT	High	High or normal	Low or low-normal	UCCR >0.01-0.02
FHH	High	Normal (High in ~20%, some with vit D deficiency)	Normal	24 hr Uca <100 mg/day, UCCR typically <0.01

- If records show history of normocalcemia in the past, it isn't FHH
- CKD, vitamin D deficiency and very low calcium intake can cause lower than expected urine calcium excretion (<200 mg/day) in PHPT
- Ask about hypercalcemia in family members
- Consider genetic testing if UCCR <0.01, or if 0.01-0.02 and dx uncertain

International workshop	2008	2013	2022
Serum calcium (>upper limit normal)	1.0 mg/dL	1.0 mg/dL	1.0 mg/dL
Skeletal	BMD by DXA ≤-2.5 or prior fragility fracture	1) BMD by DXA ≤-2.5 2) Vertebral fracture assessment	1) BMD by DXA ≤-2.5 2) Vertebral fracture assessment
Renal	eGFR <60 cc/min **24 hr urine calcium results NOT an indication for surgery**	1) CrCl <60 mL/min **2) 24 hr urine calcium >400 mg/day + increased stone risk** 3) Nephrolithiasis or nephrocalcinosis on imaging	1) CrCl <60 mL/min **2) 24 hr urine calcium >250 mg/day (women) or >300 mg/day (men)** 3) Nephrolithiasis or nephrocalcinosis on imaging
Age (years)	<50 years	<50 years	<50 years

Bilezikian JP, et al. Task Force #8: Management of Primary Hyperparathyroidism. J Bone Miner Res. 2022

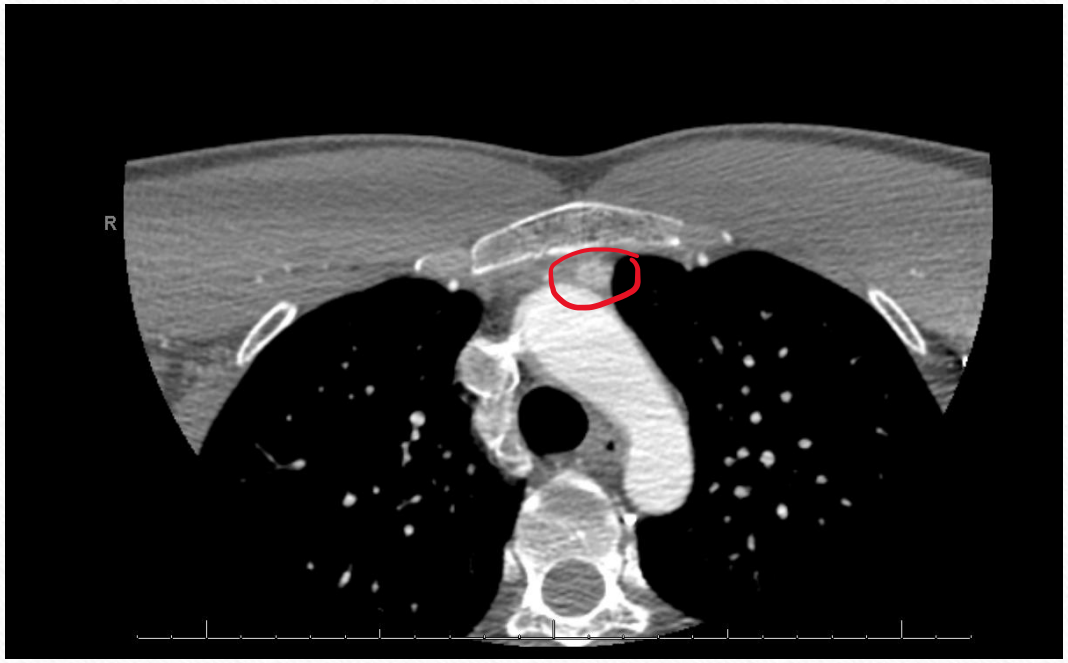
Perspectives from the Surgeon

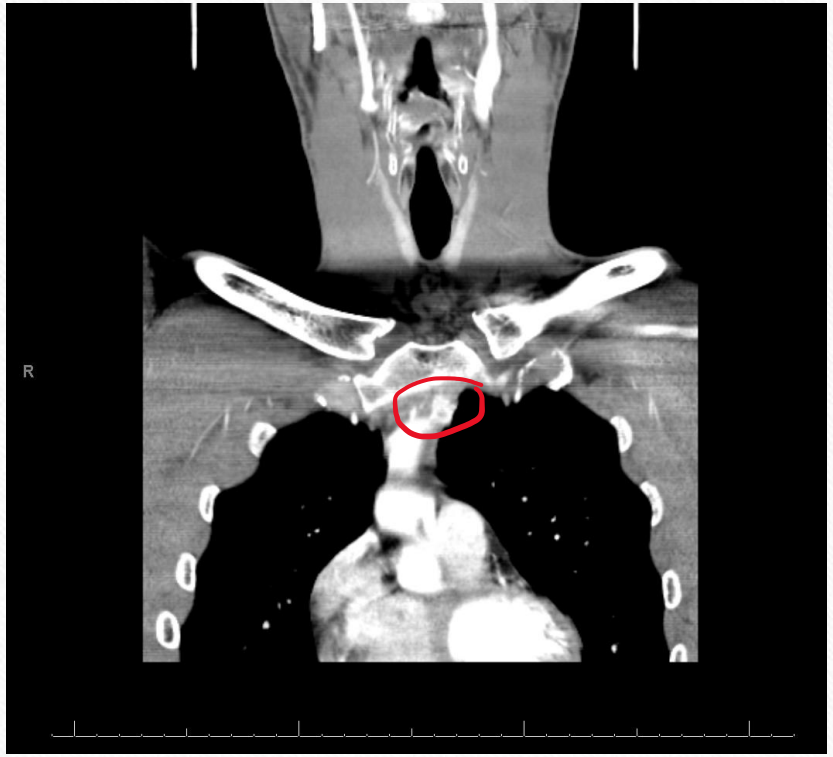
- What imaging is preferred
- What is the ideal candidate
- What are the current techniques, and what do you see as the future

Case: Where in the world…

- 31 yo male, history renal stones
- Biochemically proven pHPT
- Followed by surgeon for 2+ years with negative imaging
  - Recommendation → "yearly imaging until something is seen" per patient
- Calcium now >12.5
- Presented to me for second opinion

Imaging: substernal adenoma that was removed via a transcervical approach





Role of imaging

- **Recommendation4-1:** *Patients who are candidates for parathyroidectomy should be referred to an expert clinician to decide which imaging studies to perform based on their knowledge of regional imaging capabilities (strong recommendation; low quality evidence).*
- **Recommendation4-2:** *Patients who are candidates for surgery and have negative or discordant imaging results should still be referred to a parathyroid surgeon for evaluation (strong recommendation; low-quality evidence).*
- Role of imaging is not for diagnosis but to facilitate the conduct of surgical intervention
- Negative imaging should not influence the surgical referral
- 15% of disease is multigland, typically imaging is negative

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Concomitant Thyroid Disease

- **Recommendation 4-3:** *Cervical ultrasonography is recommended to localize parathyroid disease and assess for concomitant thyroid disease (strong recommendation; low-quality evidence).*
- **Recommendation 11-1:** *Patients undergoing parathyroidectomy should have preoperative thyroid evaluation because of the high rate of concomitant disease, which may require thyroid resection (strong recommendation; moderate-quality evidence).*
- 40-60 % of patients with parathyroid disease will have concomitant thyroid pathology on US
- ~4% of patients with thyroid disease will have parathyroid disease
- Basic work up for both if surgery is considered

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Surgical approach

- Gold standard has been bilateral 4 gland exploration
  - Many use in combination with imaging and IOPTH
- Focused minimally invasive approach: should employ IOPTH
  - Less invasive
  - Should result in fewer complications
  - Need low threshold to convert to BE
  - Same day discharge safe and encouraged
- Both with excellent rates of cure 95-99%

Surgical Complications

- Failed operation
- Hypocalcemia—transient
- Hypoparathyroidism
- Hematoma
- Infection
- Injury to the recurrent laryngeal nerve

Case: Fatigue

- 50 year old female
- Lab tech with new onset fatigue
- Had labs obtained that she requested
- Ca 9.7, PTH 136, Vit D 48, GFR >60, 24 urine for ca 502
- Nuclear medicine scan suggestive of a left inferior adenoma

Normocalcemic pHPT

- Review of the literature regarding management of normocalcemic PHPT (NPHPT) is complicated due to the lack of consistent diagnostic criteria
- Few studies measured ionized calcium
- Vitamin D deficiency be corrected before making the diagnosis of NPHPT This may result in unmasking of hypercalcemic PHPT
- Recommend a level of 30 ng/mL before a diagnosis of NPHPT is made.

Bilezikian et al Nov 2022 JBMR

Normocalcemic pHPT

- Studies have demonstrated an approximately two to threefold higher prevalence of multiglandular disease in patients with normocalcemic versus hypercalcemic disease
- Unsuccessful PTX is also more common in this form of the disease than in those with hypercalcemia.
- Panel concludes that cannot provide specific guidelines for surgery in this phenotype of the disease at this time.

Bilezikian et al Nov 2022 JBMR

Normocalcemic PHPT

- **Normocalcemic PHPT** is defined as normal serum calcium levels with elevated iPTH levels in the absence of secondary causes of HPT.
  - The definition of cure must be modified when compared to classic PHPT.
- **<u>Recommendation:</u>** In normocalcemic PHPT, the classic definition of cure as normocalcemia > 6 months after surgery should also include normalization of iPTH > 6 months. (**Insufficient evidence)**
- Consideration for surgery with caution. Candidates include worsening bone and renal disease. Typically multigland disease at time of surgery.

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Normocalcemic pHPT Management

- Rule out ALL secondary causes including renal wasting of calcium
- Fasting blood work to include ionized calcium
- Imaging should be ordered only once the decision for surgery is made
- Patients best served with coordinated multidisciplinary care
- Best to delay surgical intervention until confident diagnosis is secured and patient will benefit from surgery

Common secondary causes of elevated PTH

- Chronic kidney disease- Creatinine clearance <60 ml/min
- Medications (calcium normal or high)- Thiazide and loop diuretics, lithium
- Medications (calcium normal or low)- Foscarnet, citrate (banked blood/plasma), EDTA, bisphosphonates, denosumab, cisplatin, aromatase inhibitors
- Hypercalciuria secondary to renal leak- Renal hypercalciuria
- Malabsorption syndromes- Celiac disease, inflammatory bowel disease, gastric bypass surgery, cystic fibrosis
- Vitamin D (25-OH) deficiency/insufficiency- Deficiency commonly defined as <20 μg/L Insufficiency commonly defined as 20-30 μg/L

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Special Considerations

- Lithium induced disease
- MEN1 and MEN2
- Hyperparathyroidism-jaw tumor syndrome
- Familial isolated hyperaparathyroidism
- Parathyroid cancer
- All need to be considered prior to intervention as this can affect the planning and intervention in regards to surgery

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Questions

Case: PTH normal range

- 35 yo female
- History renal stones
- FH negative
- Ca 11.2, PTH 40, vit D 37, 24 u ca 301, GFR >60

Inappropriate suppression of PTH

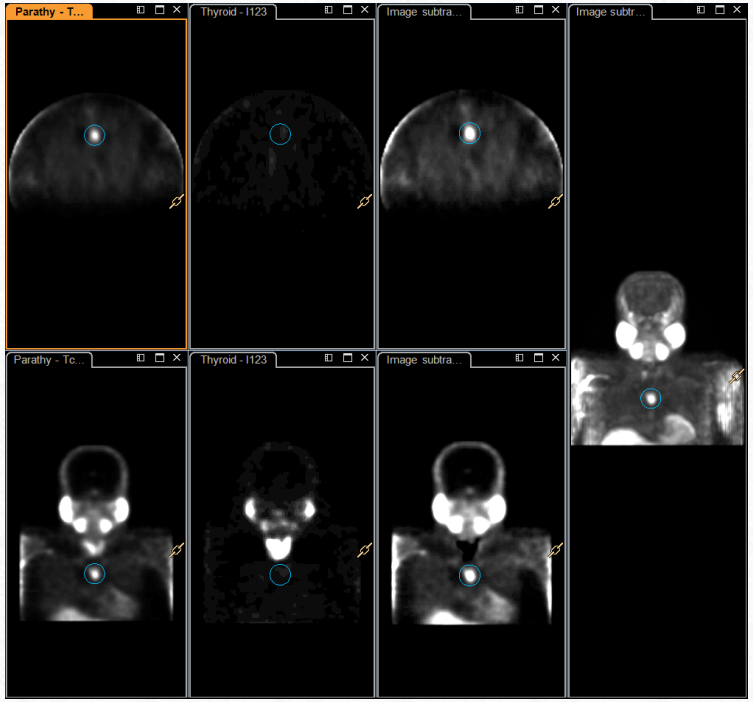
- Can see normal PTH values in primary HPT
- Normocalcemic people typically have PTH's of 25 or 30
- If you raise someone's Ca to 11.2 – the PTH should drop to <10
- If calcium is elevated and PTH is inappropriately suppressed
  - →**<u>This is PTH dependent hypercalcemia</u>**

Questions

Case: Not again

- 62 yo male with a long standing history of renal stones
- Previous parathyroid surgery 3 glands identified and removed per patient
- No op and path available for review
- Following guidelines repeat biochemical work up consistent with pHPT
  - Ca 12.5, PTH 134, GFR >60, vit d 40, 24 urine ca 306
- Vocal cord evaluation with normal movement bilaterally

Findings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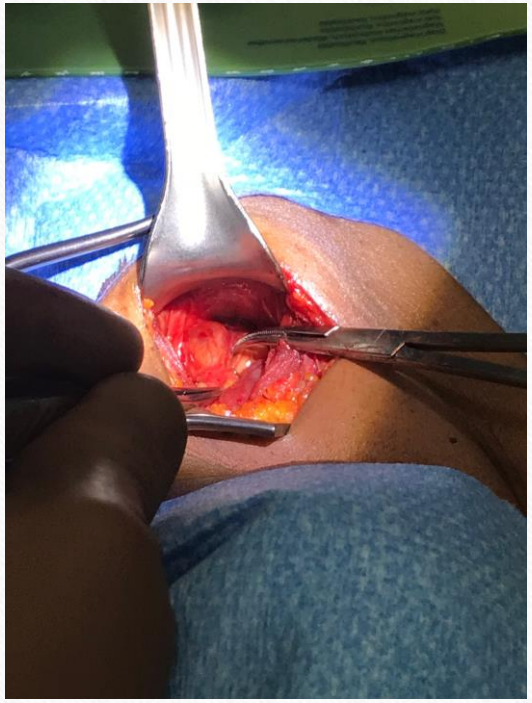

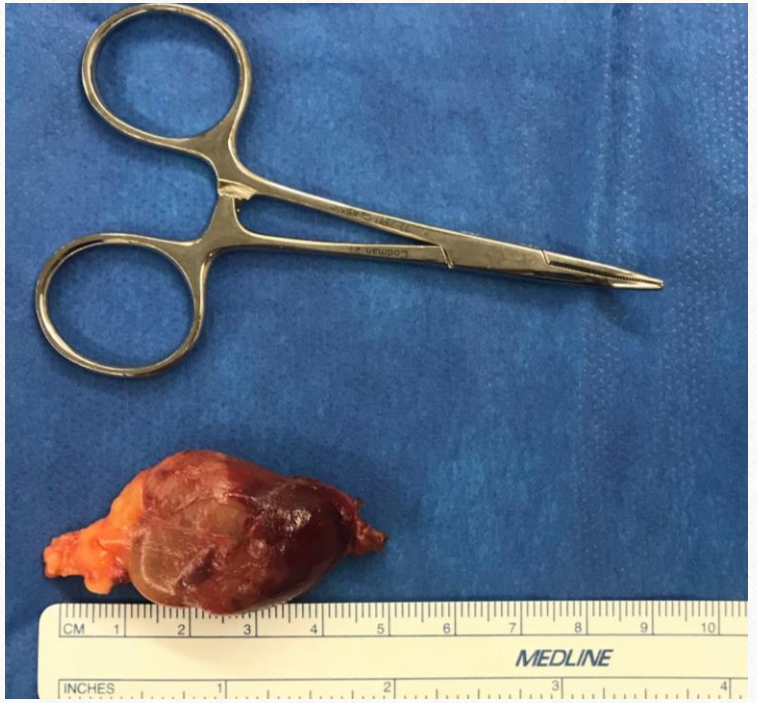
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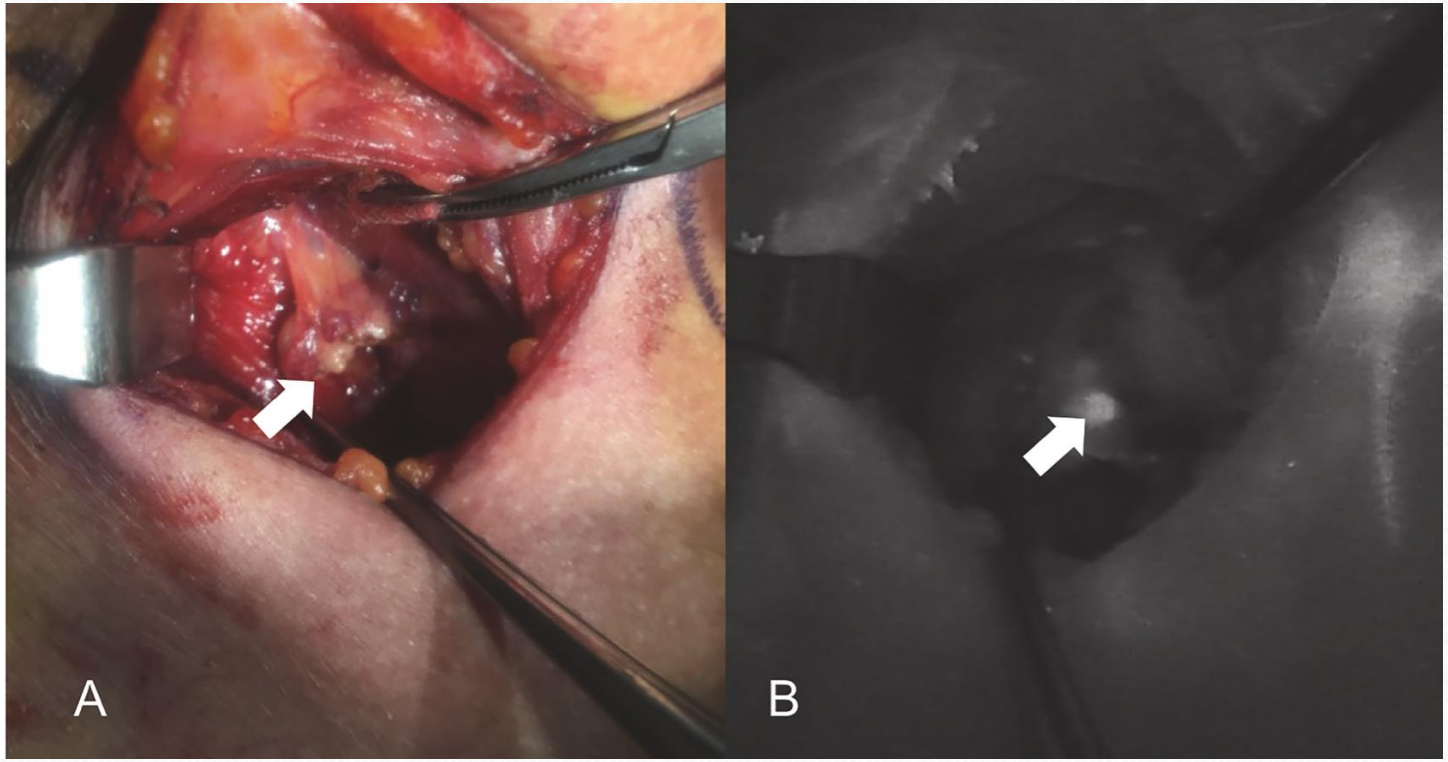
New Technology: Parathyroid Autofluorescence



Demarchi et al. Innovative Surgical Science.
https://doi.org/10.1515/iss-2021-0001

Reoperative parathyroid surgery

- Operation with previous procedure that put the RLN at risk
- **Recommendation 17-1:** *The evaluation of persistent or recurrent pHPT should include confirmation of biochemical diagnosis, assessment of indications for surgery, review of prior records if available, and evaluation of RLN function (strong recommendation; low-quality evidence).*
- Success rates 80% in expert hands (compared with 95-99% for initial procedures
  - *The surgeon who performs at least 50 parathyroidectomies per year is considered by most endocrine surgeons to be experienced* (2022 International Workgroup)
- Consider that gland removed may be last remaining gland

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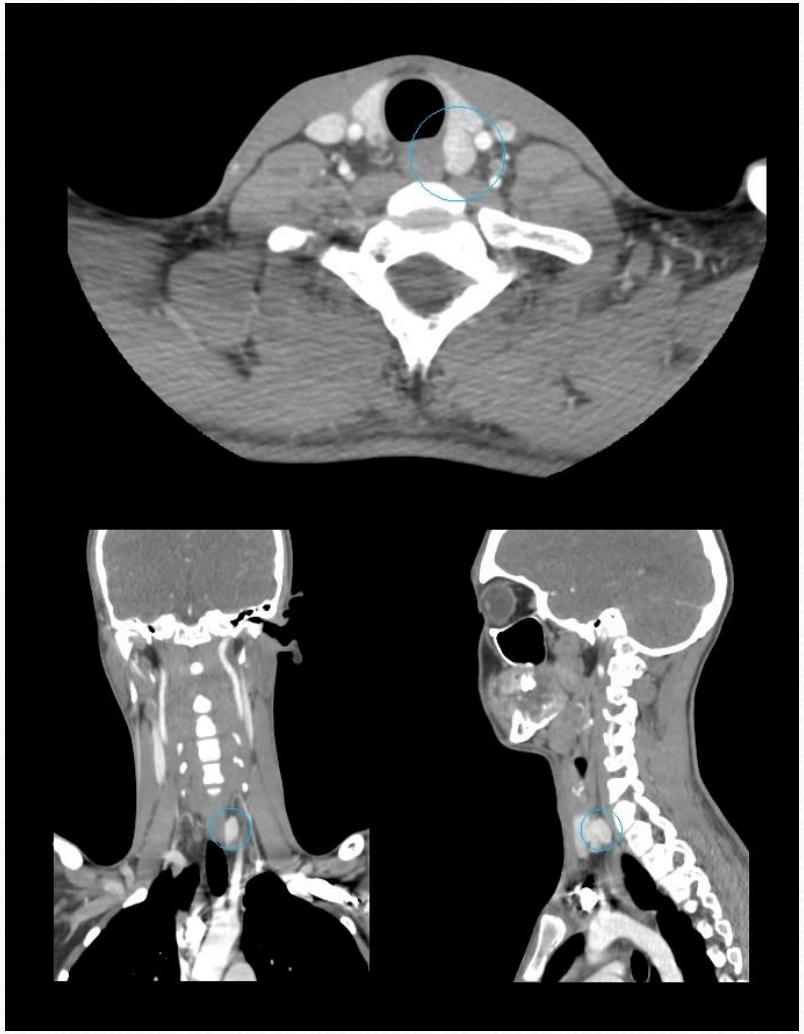
Questions

Case: Calcium Through the Roof

- 24 yo male
  - Elevated calcium (as high as 13) on perioperative blood work
- Past medical history: Renal calculi
- Family History: Negative for endocrine diseases
- Labs: Ca 13.3, PTH 843, Vit D 10, GFR nl, 24 h urine for calcium 274

Imaging

- Routine CT of neck with contrast
- Read as non localizing by radiology



Operative findings

- Minimally invasive focused approach with nerve monitoring endotracheal tube and IOPTH
  - Single gland identified
  - PTH 1328 pre op and 98 at a 10 min post excision evaluation
- Post op course delayed discharge (POD#6) due to low calcium which was symptomatic
  - Expected scenario complicated by a low Vit D pre op

Final pathology and genetic testing results

- LEFT SUPERIOR PARATHYROID, PARATHYROIDECTOMY:
  - Hypercellular and enlarged parathyroid (wt 2.86 g)
- **Recommendation 1-6:** *Genetic counseling should be performed for patients younger than 40 years with pHPT and multigland disease (MGD) and considered for those with a family history or syndromic manifestations (strong recommendation; low-quality evidence).*
- Post op genetic testing: RET c.1998G>T (p.Lys666Asn)→**MEN2a**
  - **Ultimately returned to OR for prophylactic thyroidectomy; normal PTH/Ca post op**
- Family tested as well with other members positive

Questions

Hypoparathyroidism

- Rare disorder of mineral metabolism characterized by hypocalcemia and absent or deficient production of PTH
- Calcium-conserving effects of PTH on the renal tubule are lost
- Phosphaturic effects of PTH is lost

Types/causes

- ***Post surgical hypopatharyroidism***
- Autoimmune hypoparathyroidism
- Congenital hypoparathyroidism
- Pseudohypoparathyroidism
- Misc. causes of hypoparathyroidism

Post-surgical Hypoparathyrodism

- Most common acquired hypoparathyroidism
- A study showed Incidence of transient and permanent hypoparathyroidism was 7.3% and 1.5%
- Extent of resection and surgical technique had a greater impact on the rates of permanent postoperative hypoparathyroidism than thyroid pathologic condition
- At least 2 parathyroid glands should be identified and preserved
- High volume surgeons less risk of complications→ >50 cases per year

Thomusch O et al. *Surgery*. 2003;133(2)

Post-surgical Hypoparathyrodism

- De-escalation of surgical intervention
- 2 fold increased risk of mortality when occurs after total thyroidectomy for benign disease
- Intact PTH level post op to identify those at risk
- Be aware of and prepare for those patients at risk

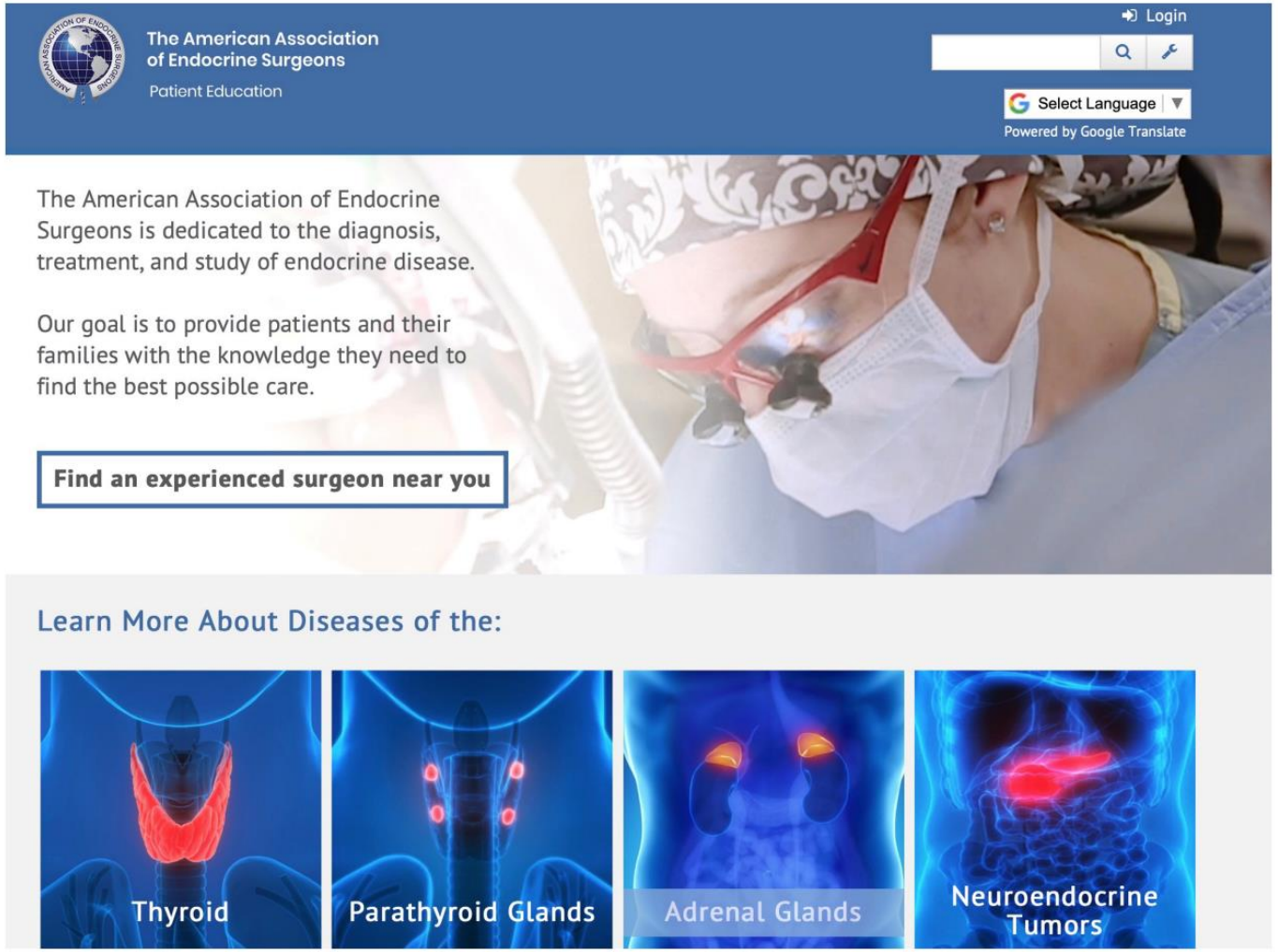
Treatment of symptomatic hypocalcemia

- Can be a medical emergency requiring acute IV calcium gluconate
- Actual value of the corrected serum calcium level is often regarded as a threshold for acute management [7.5 mg/dL]
- IV calcium gluconate to reverse symptoms, oral supplements with calcium and rocalcitriol
- Calcium chloride - avoid, irritating and potentially sclerosing to veins

Treatment option on the horizon

Indications for Considering the Use of rhPTH (1-84) in Hypoparathyroidism
1. Inadequate control of the serum calcium concentration (this could be due to intercurrent illness, compliance, absorption, or intrinsic changes in requirements that are beyond facile correction with calcium and active vitamin D)
2. Oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 µg of active vitamin D or >3.0 µg of the 1-α vitamin D analog
3. Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 mL/min)
4. Hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg[b]/dL[b] (4.4 mmol[b]/L[b])
5. A gastrointestinal tract disorder that is associated with malabsorption
6. Reduced quality of life

Brandi ML et al. *The Journal of Clinical Endocrinology & Metabolism*, Volume 101, Issue 6, 1 June 2016



http://www.endocrinediseases.org

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Questions