Patient SH

60yM presented to local ED with 4 weeks of extreme fatigue.

Over the course of 1 year, he had increasing fatigue which he attributed to aging. Took early retirement, but had progressive worsening fatigue over last 4 weeks.
Patient SH

On evaluation, found to have:

- Calcium: 17 mg/dl (normal ~8.5-10.3)
- PTH: 1558 pg/ml (normal ~15-65)
What is hyperparathyroidism?

- Inappropriately elevated parathyroid hormone level
- Classically associated with hypercalcemia
- ~10% may present with “normocalcemic hyperparathyroidism”
“Bones, stones, groans, moans, psychiatric overtones”
Causes of hyperparathyroidism

- Primary – PTH oversecretion by abnormal parathyroid(s)
  - 85% single parathyroid adenoma
  - ~15% multigland disease (double adenoma or hyperplasia)
  - <1% parathyroid carcinoma

- Secondary – PTH oversecretion secondary to hypocalcemia
  - Vitamin D deficiency
  - End stage renal disease

- Tertiary – autonomous PTH oversecretion due to loss of CaSR
  - ESRD s/p transplant
Biochemical profiles

- **Primary hyperparathyroidism**
  - High PTH (usually in 100’s)
  - High calcium (in >90% of patients)

- **Secondary hyperparathyroidism due to ESRD**
  - Extremely high PTH (usually in 1000’s)
  - Low calcium
  - High calcium-phos product (>55 associated with high risk for calciphylaxis)

- **Tertiary hyperparathyroidism**
  - Extremely high PTH (usually in 1000’s)
  - High calcium
Role of surgery

- **Primary hyperparathyroidism**
  - Surgery is only curative treatment
  - Bisphosphonates may help manage hypercalcemia
  - Calcimimetics not indicated

- **Secondary hyperparathyroidism due to ESRD**
  - Usually managed with calcimimetics (cinacalcet)
  - Surgery indicated when patients intolerant or non-compliant with calcimimetics, or for severe disease
  - Surgery is subtotal parathyroidectomy or total parathyroidectomy with autograft

- **Tertiary hyperparathyroidism**
  - Surgery indicated for hypercalcemia; may improve graft survival
  - Surgery is subtotal parathyroidectomy
Primary hyperparathyroidism

- Surgery indicated for symptoms
- Surgery indicated for asymptomatic patients with evidence of severe disease or evidence of end organ dysfunction
Table 1. Guidelines for Surgery in Asymptomatic PHPT: A Comparison of Current Recommendations With Previous Ones

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>2002</th>
<th>2008</th>
<th>2013</th>
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<tr>
<td><strong>Measurement</strong></td>
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<td>Serum calcium</td>
<td>1–1.6 mg/dL (0.25–0.4 mmol/L)</td>
<td>1.0 mg/dL (0.25 mmol/L)</td>
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<td>Skeletal</td>
<td>BMD by DXA: Z-score</td>
<td>BMD by DXA: T-score</td>
<td>BMD by DXA: T-score</td>
<td>A. BMD by DXA: T-score</td>
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<td>&lt;−2.0 (site unspecified)</td>
<td>&lt;−2.5 at any site&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;−2.5 at any site&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;−2.5 at lumbar spine, total spine, total hip, femoral neck, or distal 1/3 radius&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Renal</td>
<td>A. eGFR reduced by</td>
<td>A. eGFR reduced by</td>
<td>A. eGFR &lt; 60 cc/min</td>
<td>A. Creatinine clearance</td>
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<td>&gt;30% from expected</td>
<td>&gt;30% from expected</td>
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<td>&lt; 60 cc/min</td>
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<td>B. 24-h urine for</td>
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<td>calcium &gt;400 mg/d (&gt;10 mmol/d)</td>
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<td>C. Presence of nephrolithiasis or</td>
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<td>nephrocalcinosis by</td>
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<td>Age, y</td>
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Patient SH

60yM presented to local ED with 4 weeks of extreme fatigue. +Depression, bone pain. Denied constipation, memory difficulties, nephrolithiasis.

On evaluation, found to have calcium level 17 mg/dl, PTH 1558 pg/ml, Cr 2.4 mg/dl. Also mild elevation in LFTs. Normal Vit D. (One year prior, Ca was 11.3 and Cr 0.9)

- PMH: Hypercalcemia
- PSH: Hernia repair
- HM: None
- All: NKDA

- FH: Sister with primary hyperparathyroidism
Evaluation of primary hyperparathyroidism

- Biochemical
  - PTH
  - Calcium
  - Vitamin D
  - Creatinine
  - 24 hour urine calcium

- Imaging
  - DEXA scan
  - Thyroid ultrasound
  - Technitium 99 sestamibi scan
Patient SH

- **Biochemical:**
  - PTH: 1558 pg/ml (normal 10-60)
  - Calcium: 17 mg/dl (normal 8.5-10.5)
  - Vit D: WNL
  - Creatinine: 2.4 mg/dl (normal 0.6-1.5)
  - 24 hour urine calcium: 614 (normal 100-321 mg/24 hr)

- **Imaging:**
  - DEXA: WNL
  - Sestamibi: Localized to left inferior neck
  - Ultrasound: Normal thyroid. 3 cm hypoechoic lesion inferior to the left inferior pole of the thyroid
Hypercalcemic crisis

- Variably defined as adjusted calcium >13.5-14 mg/dL with signs & symptoms of hypercalcemia
- ~1.6-6% of patients present with hypercalcemic crisis
- Causes of hypercalcemic crisis:
  - Adenoma 85-88%
  - Multigland hyperplasia: 5-10%
  - Parathyroid cyst: 0-5%
  - Parathyroid carcinoma: 4.5-5%

Phitayakorn et al. JACS. 2007.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Drugs</th>
<th>Specific Indication</th>
<th>Dose</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
</tr>
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<tbody>
<tr>
<td>Volume repletion</td>
<td>0.9% NS</td>
<td>Dehydration</td>
<td>2 to 4 liters per day, with goal urine output &gt; 2 L/day</td>
<td>Increases filtration of calcium by increasing GFR, decreases proximal tubular reabsorption and promotes calcuiuria in kidneys</td>
<td>Fluid overload, CHF exacerbation in patients with compromised cardiac or renal function</td>
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<td>Diuresis</td>
<td>Loop diuretics like furosemide</td>
<td>Fluid overload</td>
<td>40 mg to 80 mg up to 500 mg/day</td>
<td>Blocks calcium reabsorption in loop of Henle</td>
<td>Dehydration, electrolyte abnormalities like hypokalemia</td>
</tr>
<tr>
<td>Intravenous Bisphosphonate</td>
<td>Pamidronate</td>
<td>HC in addition to IVF and diuresis</td>
<td>60 mg to 90 mg IV over a period of 2 hours</td>
<td>Inhibits FPPS enzyme of mevalonate pathway in osteoclast.</td>
<td>Severe musculoskeletal pain, renal failure</td>
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<tr>
<td></td>
<td>Zoledronate</td>
<td>As above</td>
<td>4 mg to 8 mg IV over a period of 15 minutes</td>
<td>As above</td>
<td>As above, flu-like syndrome, and atrial fibrillation</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Hemodialysis or peritoneal dialysis</td>
<td>HC with renal failure, heart failure when above treatment modalities are contraindicated</td>
<td>Calcium free dialysate</td>
<td>Removes calcium from circulation</td>
<td>Dialysis-related complications like hypovolemia, hypotension</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; GFR = glomerular filtration rate; FPPS = farnesyl pyrophosphate synthase; HC = hypercalcemic crisis; IV = intravenous; IVF = intravenous fluids; NS = normal saline.
SH Hospital course

- Hospitalized for 4 days
- Received:
  - Fluid resuscitation
  - Pamidronate
  - Calcitonin 270 units x 4 doses
- Discharged with a calcium of 11.1 mg/dl and a creatinine of 1.9 as well as improved transaminitis
SH Operative course

- Planned for parathyroidectomy ± left thyroid lobectomy depending on intraoperative concern for parathyroid carcinoma
- Intraoperatively, very large left parathyroid adenoma, adherent to thyroid gland and concerning for parathyroid carcinoma
- Parathyroidectomy and left thyroid lobectomy performed uneventfully
- IOPTH decrease to 103 pg/ml, >95% decrease
IOPTH

- Rapid PTH assay
- Intraoperative “cure” – IOPTH decreases 50% (some say final IOPTH needs to be into normal range)
SH Post operative course

- Calcium: 8.8 mg/dL; discharged on calcium 500mg QID, vitamin D 2000U QD
- Plan to recheck calcium and PTH in 6 mo
Post-operative care after parathyroidectomy

- Calcium repletion (calcium carbonate or calcium citrate)
- Calcitriol if symptomatic

- Sample regimen: Elemental calcium 600 mg (two extra strength tums) TID with calcitriol 0.25mcg daily

- Patient education on symptoms of hypocalcemia
  - Perioral/hand numbness or tingling
  - Chvostek’s sign – twitching of facial muscles after tapping on facial nerve
  - Trousseau’s sign – muscle contraction of finger extensors after compression with BP cuff or pressure
A 23 year-old man presented to his local emergency department with a femur fracture after a fall from standing. History was significant for pediatric liver transplant, with subsequent end stage renal disease caused by immunosuppressive medications, on hemodialysis.

- **PMH:** Primary sclerosing cholangitis, ESRD, CHF, Seizure disorder, hypertension, substance abuse, ITP, asthma, GERD
- **PSH:** Liver transplant (2002)
- **HM:** Albuterol, atorvastatin, carvedilol, cinacalcet, clonidine, clopidogrel, folic acid, hydralazine, isosorbide monitrate, levetiracetam, lisinopril, nifedipine, sevelamer, sirolimus
- **All:** Acetaminophen
Biochemical studies

- **Outpatient**
  - PTH: 1781 pg/mL (peak value 2362 pg/mL)
  - Per nephrology notes, normocalcemic

- **On admission:**
  - Calcium: 9.4 mg/dL → started on cinacalcet
  - Alkaline phosphatase: 751 IU/L (normal 44-147)
  - Phosphate: 4.8 mg/dL (normal 2.5-4.5)
  - Ionized Calcium: 1.15 mmol/L (normal 1.1-1.35)

- **On transfer:**
  - Calcium: 6.9 mg/dL
  - PTH 466 pg/mL
7x8x9 mm lesion in the inferior right pole of the thyroid and a 9x8x17 mm lesion in the inferior right pole of the thyroid
Preoperative Sestamibi
Initial intraop PTH: 225 pg/ml

Right superior

Right inferior, 5% biopsy

Left supernumerary

Left superior, 5% biopsy

Left inferior
IOPTH

- Baseline PTH: 225 pg/ml
- PTH 15 min after resection: 139 pg/ml
- Repeat post-resection PTH: 138 pg/ml
What to do next?

Re-explore:
- Skeletonize the laryngeal nerves bilaterally
- Dissect the thymus and examine it for glands

Still negative.

Call for intraoperative ultrasound!
Intraoperative Ultrasound

Radiology identified a 11 mm intrathyroidal parathyroid in the right medial lobe

Final PTH: 49 pg/ml
Right superior 384 mg
Right intra-thyroidal 437 mg
Right inferior, 5% biopsy 8 mg
25% left in situ

Left superior, 5% biopsy 13 mg
Left supernumerary 150 mg
Remainder → Cryopreserved
Left inferior 953 mg
Postoperatively

- Initially hypocalcemic to 6.3 mg/dL (corrected 7.4 mg/dL)
- Three days of calcium infusion
- Discharged POD7 with calcium 8.3 mg/dL (corrected 9.1 mg/dL) on oral regimen of calcium acetate and calcitriol
Ectopic and supernumerary parathyroids

- Most commonly 4 parathyroids
- Ectopic parathyroids present in 5-7% of patients
- Supernumerary parathyroids particularly common in patients with secondary hyperparathyroidism (~13-30%)

Role for IOPTH Monitoring

- No current standard criterion for IOPTH in SHPT patients
  - PTH cleared by kidneys, so kinetics uncertain in ESRD

- STARD Study
  - >70% decrease considered successful operation
  - <60 pg/mL PTH on POD1 was considered to predict cure
Treatment goals - SHPT

- Goal PTH in Stage 5 CKD: 150-300 pg/mL
- Significant increase in all-cause mortality with PTH>600 pg/mL
- Parathyroidectomy may decrease fractures, decrease calciphylaxis, improve symptoms
- Parathyroidectomy demonstrates a survival benefit in ESRD patients on dialysis (20% reduction in risk of death)

Shindo et al. JACS. 2016.
Operative strategies

- **Subtotal parathyroidectomy**: Resection of 3 complete glands, partial resection of most normal gland, preserving pedicled remnant
- **Total parathyroidectomy with autotransplant**: Resection of all parathyroid tissue, with autotransplant of tissue into SCM or forearm
- **Total parathyroidectomy without autotransplant**: Resection of all parathyroid tissue
Hungry bone syndrome

- Abrupt decrease in PTH leads to net influx of calcium, phosphate, and magnesium into bone
- Characterized by hypocalcemia, hypomagnesemia, hypophosphatemia, hyperkalemia
- Management: IV calcium, magnesium, phos; dialysis
- Most common in patients with pre-existing bone disease, and ESRD (up to 20%) 
- Other risk factors: older age, larger parathyroid volume resected, higher BUN, alk phos
Summary

- **Primary hyperparathyroidism**
  - High PTH, usually high calcium
  - 85% single adenoma, 15% multigland disease
  - Surgery is only curative treatment!
  - Ectopic and supernumerary glands in 5-7% of patients
  - IOPTH needs to fall >50% (Miami Criteria)
  - Final cure is defined as normocalcemic/normo parathyroid 6 months after surgery
Summary

- **Secondary hyperparathyroidism**
  - Most commonly Vit D deficiency -> treat with Vit D (no surgery!)
  - When due to ESRD: extremely elevated PTH, low calcium
  - First line tx: calcimimetics (cinacalcet) and phosphate binders
  - Surgery indicated when patients intolerant or non-compliant with calcimimetics, or for severe disease (calcium-phos product >55)
  - Surgery is subtotal parathyroidectomy or total parathyroidectomy with autograft
  - No clear cut IOPTH guidelines, but final IOPTH <60 pg/ml may predict lower recurrent/persistent hyperparathyroidism
Summary

- **Tertiary hyperparathyroidism**
  - Extremely elevated PTH, high calcium
  - Due to autonomous secretion of PTH, usually after renal txp for ESRD
  - Surgery indicated for hypercalcemia to improve graft survival
  - Surgery is subtotal parathyroidectomy
  - No clear cut IOPTH guidelines, but final IOPTH 100-200 pg/ml may predict lower recurrent/persistent hyperparathyroidism
Question 1

Which of the following is true regarding the parathyroid glands?

A. The inferior glands arise from the fourth branchial pouch and the superior ones from the third pouch
B. The superior glands are more likely to be found in an ectopic position
C. The superior glands are more likely to be found in the thymus
D. Three glands are more common than five glands
E. Ectopic superior glands are more likely to be found in the retro- or paraesophageal space
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During neck exploration for primary hyperparathyroidism, only 3 parathyroid glands are identified, all of which appear to be normal. Which of the following would be appropriate?

A. Perform a transcervical thymectomy
B. Removal all 3 glands and reimplant one in the forearm
C. Remove 2 and a half glands and then close
D. Perform a median sternotomy to look for ectopic parathyroid
E. Obtain biopsy samples of all 3 parathyroid glands and then close
Question 2

During neck exploration for primary hyperparathyroidism, only 3 parathyroid glands are identified, all of which appear to be normal. Which of the following would be appropriate?

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B. Removal all 3 glands and reimplant one in the forearm
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E. Obtain biopsy samples of all 3 parathyroid glands and then close
Question 3

A 50 year old woman presents to the emergency department with nausea, anorexia, irritability, and a serum calcium level of 14.5 mg/dl. Initial management is:

A. Emergent parathyroidectomy
B. Furosemide
C. IV saline
D. Mithramycin
E. Calcitonin
A 50 year old woman presents to the emergency department with nausea, anorexia, irritability, and a serum calcium level of 14.5 mg/dl. Initial management is:

A. Emergent parathyroidectomy
B. Furosemide
C. IV saline
D. Mithramycin
E. Calcitonin
Question 4

A 60 year old woman presents with a history of kidney stones and a firm, palpable neck mass. Her serum calcium level is 14.1 mg/dl. The most likely diagnosis is:

A. Parathyroid adenoma
B. Parathyroid hyperplasia
C. Parathyroid cancer
D. Breast cancer with bone metastasis
E. Secondary hyperparathyroidism
Question 4

A 60 year old woman presents with a history of kidney stones and a firm, palpable neck mass. Her serum calcium level is 14.1 mg/dl. The most likely diagnosis is:

A. Parathyroid adenoma
B. Parathyroid hyperplasia
C. Parathyroid cancer
D. Breast cancer with bone metastasis
E. Secondary hyperparathyroidism

- 70yM found to be hypercalcemic on routine labs
- +Nephrolithiasis, no known hx of BMD loss, -neurocognitive sx
- PTH 207 (normal 8-54)
- Calcium 11.7
- Creatinine 1.4
- iCa: 6.9 (normal 4.5-5.6)
- Vit D normal per pt
- DEXA: Not performed
- US: Non localizing
- Sestamibi: Localized to left
Thank you!

(Good luck this weekend!)