“83 Year-old Woman Presenting with Altered Mental Status and Hypercalcemia”

Dr. Dickens does not have any relevant financial relationships with any commercial interests.
Objectives

1. Review presentation of and diagnostic approach to hypercalcemia
2. Discuss management of severe hypercalcemia and evidence for use of loop diuretics
3. Evaluate evidence for vitamin D replacement in primary hyperparathyroidism
4. Review pre-operative localization studies in primary hyperparathyroidism and incidence of ectopic parathyroid adenomas
Chief complaint

83 year old woman with a PMH of CVA, HTN, and complete heart block s/p pacemaker presents to the ER with lip swelling and altered mental status.
HPI: Patient lives in a nursing home since a recent admission for CVA and on the morning of admission was noted to have new lip lesions and swelling. She was also somnolent and less interactive than usual (baseline AAOx1, interactive).

PMH: CVA one month ago, HTN, complete heart block s/p pacemaker

PSH: None

ROS: Unable to obtain

Meds:
- Aspirin 81mg daily
- Atorvastatin 80mg daily
- Fluconazole 200mg
- Nystatin oral swish

Social Hx: No T/E/D. Lived with family until recent admission with CVA, since then has been in a nursing home.

Family Hx: Unable to obtain
Physical exam

VITALS: Temp 36.6, BP 106/67, HR 83, RR 22, O2 sat 98 on 2L NC, BMI 24.2

**General:** Not in distress

**ENT:** Erythematous papules and open pustules on the lip and R chin with yellow crusting. Whitish/yellow thick coating on tongue and lower gums. Three small white lesions on L lower lip. Raised erythematous welts on R cheek

**CV:** Regular rhythm and rate, no murmurs, rubs, or gallops

**Pulmonary:** Clear to auscultation bilaterally with poor effort

**GI:** Normoactive bowel sounds, not visibly distended, **RUQ tenderness.** No mass. No hepatosplenomegaly

**GU:** No suprapubic tenderness. Foley in place draining clear yellow urine

**MSK:** Edema in bilateral lower extremities (R>L) with venous stasis skin changes. Decreased bulk and tone

**Neuro:** Somnolent. Opens eyes to verbal stimuli, withdraws to pain in all extremities. Intermittently follows one step commands. RUE contracted with spasticity and increased tone. R facial droop. Myoclonus in the bilateral upper extremities

**Skin:** Sacrum with erythema, no ulceration
Admission Labs

Neutrophils 76%

Ca 14.0
Mg 2.2
Ph 2.2

Cr baseline 0.5-0.7

EKG: NSR, nonspecific ST abnormality, QTc 430
Lactic acid= 1.6
Troponin= <0.03
TSH= 0.63

Blood cultures x2: pending
UA: Negative LE, negative nitrites, 1+ ketones, occasional WBC, no bacteria, many hyaline casts
Hypercalcemia

- **Presentation**: anorexia, N/V, pancreatitis, AKI, weakness, AMS, shortened QT interval
- **Severity**:  
  - Mild Ca <12  
  - Moderate Ca 12-14  
  - Severe Ca >14  
- **Etiology**: 90% is caused by primary hyperparathyroidism or malignancy

<table>
<thead>
<tr>
<th>Table 1 Causes of Hypercalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parathyroid disease</strong></td>
</tr>
</tbody>
</table>
| Primary hyperparathyroidism due to benign PTH adenoma, PTH carcinoma, or PTH multiglandular hyperplasia as part of multiple endocrine neoplasia syndromes  
Tertiary hyperparathyroidism |
| **Malignancy** |
| Parathyroid hormone related protein (humoral hypercalcemia of malignancy)  
Local osteolysis mediated by cytokine release  
Lytic bone metastasis  
Multiple myeloma  
Ectopic production of 1, 25 dihydroxyvitamin D by the tumor (eg, lymphoma) |
| **Endocrinopathies** |
| Adrenal insufficiency  
MEN 1, 2A  
Thyrotoxicosis  
Pheochromocytoma  
VIPoma |
| **Granulomatous disease** |
| Tuberculosis  
Sarcoidosis  
Endemic mycosis: histoplasmosis, coccidioidomycosis  
Leprosy  
Crohn’s disease  
Berylliosis |
| **Medications** |
| Estrogens  
Lithium  
Thiazide diuretics  
Excess vitamin D or vitamin A ingestion |
| **Miscellaneous** |
| Familial hypocalciuric hypercalcemia  
Immobilization |

• Additional labs
  – PTH = 356
  – 25-OH vitamin D = 13
  – 1,25-Dihydroxy vitamin D = 19
  – PTHrP = 0.4
  – SPEP = normal
• Hydration with 1L NS, then maintenance fluids at 83cc/hour
• Ca 14.0 -> 12.9 -> 12.3 -> 12.4
Management of hypercalcemia

• Goals of management
  – Lower calcium
  – Correct dehydration
  – Decrease osteoclast-mediated bone resorption
  – ** treat underlying etiology
• Emergent management:
  – IV 0.9%NS 4-6L over 24 hours → expect a 1.6-2.4 mg/dL reduction with IVF
  – Loop diuretics only if volume overload develops
  – Consider IV bisphosphonates
    • Zoledronic acid 4mg over 15min
    • Pamidronate 30–90mg (depending on severity of hypercalcaemia) at 20mg/h
    • Ibandronic acid 2–4mg
  – Second line treatments
    • Glucocorticoids
    • Calcimimetics, denosumab, calcitonin
    • Parathyroidectomy

Loop diuretics in hypercalcemia

- Mechanism: block Ca re-absorption in the ascending limb of the loop of Henle to induce calciuresis
- Review in 2008 assessed the evidence for “forced saline diuresis” in hypercalcemia and current clinical recommendations
  - Fourteen articles, most recent in 1983
  - Average furosemide dose 1120mg over 24 hours (range 240mg – 2400mg)
  - Normalization of Ca in 14 of 39 cases, but only occurred rapidly in 2 patients (within 6-12 hours)
  - Significant complications

“Furosemide should be relegated to the management of fluid overload, which should be rare if one focuses on appropriate rehydration rather than trying to induce forced diuresis.”

<table>
<thead>
<tr>
<th>Source (Reference)</th>
<th>Fluid</th>
<th>Furosemide</th>
<th>Bisphosphonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Medicine Manual (26)</td>
<td>Normal saline, 5–10 L</td>
<td>Yes, 40 mg</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Tintanalli’s Emergency Medicine: A Comprehensive Study Guide (27)</td>
<td>Normal saline volume repletion</td>
<td>Yes, 40–100 mg every 2–4 h</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Harrison’s Principles of Internal Medicine (28)</td>
<td>Normal saline, 4–6 L over 24 h</td>
<td>Yes; no dose given</td>
<td>Should be considered for patients with cancer</td>
</tr>
<tr>
<td>Current Medicine 2008 (29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Anesthesia of Principles of Clinician’s Practice (30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACP Medicine 2008 (31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cecil Medicine (35)</td>
<td>Normal saline, 200–300 mL/h</td>
<td>Yes; no dose given</td>
<td>Standard for cancer-associated hypercalcemia</td>
</tr>
<tr>
<td>Brenner &amp; Rector’s The Kidney (36)</td>
<td>Normal saline</td>
<td>Yes, no dose given, strong fluid statement</td>
<td>May be reasonable</td>
</tr>
<tr>
<td>Greenspan’s Basic and Clinical Endocrinology (37)</td>
<td>Normal saline, 500–1000 mL in the first hour, then 25–500 mL/h</td>
<td>Yes, to avoid fluid overload</td>
<td>First choice for most patients after initial therapy</td>
</tr>
<tr>
<td>Clinical Oncology (38)</td>
<td>Normal saline</td>
<td>Reserved for fluid overload</td>
<td>Mainstay of therapy</td>
</tr>
<tr>
<td>Washington Manual of Medical Therapeutics (39)</td>
<td>Normal saline, 3–4 L in first 24 h</td>
<td>No, except for fluid overload</td>
<td>Administer early</td>
</tr>
<tr>
<td>Hospital Medicine (40)</td>
<td>Normal saline</td>
<td>“Contraindicated” unless fluid overload</td>
<td>Primary therapy with fluids</td>
</tr>
<tr>
<td>UptoDate (41)</td>
<td>Normal saline</td>
<td>Loop diuretic “out of favor”; use for overload</td>
<td>Concurrent with saline</td>
</tr>
</tbody>
</table>

“First-line therapy is aggressive intravenous fluid resuscitation. Once the patient is volume replete, an intravenous loop diuretic should be added if the calcium level has not normalized.” – MKSAP 17
Back to our patient: AMS evaluation

- CXR = Marked interval improvement in patchy bilateral airspace opacities with residual diffuse interstitial opacity suggestive of edema and possibly fibrosis
- CT head = chronic subdural hematoma (stable from prior imaging), age-indeterminate small vessel ischemic disease
- EEG = no seizures
- Oral lesion swab positive for HSV-1
- Cheek lesion swab positive for VZV
- CSF examination
  - 102 WBC (81% lymph, 0% neut), 9 RBC
  - Glucose 60, Protein 50
  - Bacterial and fungal cultures negative, HSV negative, VZV positive, enterovirus negative, VDRL negative, cryptococcus negative
Management

- **Hypercalcemia**
  - Hydration with maintenance IVF, free water flushes via dobbhoff tube
  - Pamidronate 30mg x1
  - Cinacalcet 30mg BID -> uptitrated to 90mg TID

- **Vitamin D deficiency**
  - D3 1,000 IU daily

- **VZV encephalitis**
  - IV acyclovir
  - Clindamycin (for overlying impetigo)
Vitamin D deficiency in hyperparathyroidism


**TABLE 1. Baseline characteristics of patients with primary hyperparathyroidism**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>2/19</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68.3 ± 12.7</td>
</tr>
<tr>
<td>Serum calcium (mg/dl) [mmol/liter]</td>
<td>10.8 ± 0.5 [2.70 ± 0.12]</td>
</tr>
<tr>
<td>Serum phosphate (mg/dl) [mmol/liter]</td>
<td>2.8 ± 0.6 [0.89 ± 0.19]</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl) [mmol/liter]</td>
<td>0.92 ± 0.23 [0.08 ± 0.02]</td>
</tr>
<tr>
<td>PTH (pg/ml) [pmol/liter]</td>
<td>138 ± 79 [12.4 ± 7.1]</td>
</tr>
<tr>
<td>Serum 25(OH)D (µg/liter) [nmol/liter]</td>
<td>11 ± 5 [28 ± 13]</td>
</tr>
<tr>
<td>Serum 1,25(OH)₂D (pg/ml) [pmol/liter]</td>
<td>54 ± 25 [134 ± 62]</td>
</tr>
<tr>
<td>Serum ALP (U/liter)</td>
<td>105 ± 29</td>
</tr>
<tr>
<td>Urine N-telopeptides (nmol BCE/mmol creatinine)</td>
<td>54 ± 25</td>
</tr>
<tr>
<td>24-h urinary calcium (mg/d) [mmol/d]</td>
<td>232 ± 148 [5.8 ± 3.7]</td>
</tr>
<tr>
<td>L1-L4 BMD (g/cm²)</td>
<td>1.02 ± 0.16</td>
</tr>
<tr>
<td>L1-L4 BMD (T score)</td>
<td>-1.4 ± 1.3</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²)</td>
<td>0.78 ± 0.18</td>
</tr>
<tr>
<td>Femoral neck BMD (T score)</td>
<td>-1.7 ± 1.5</td>
</tr>
</tbody>
</table>

Data are mean ± sd. M, Male; F, female.
Meta-analysis: vitamin D repletion in PHPT

<table>
<thead>
<tr>
<th>First author, year, ref no</th>
<th>Study type</th>
<th>Country</th>
<th>Number of participants</th>
<th>Mean age</th>
<th>Mean pre/post 25(OH)D [nmol/L]</th>
<th>Mean (SD) Serum PTH level [pmol/l]</th>
<th>Mean (SD) Serum Calcium level [mmol/l]</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoCascio, 1985¹⁴</td>
<td>Obs.</td>
<td>Italy</td>
<td>6</td>
<td>28–51*</td>
<td>38.3/265.2</td>
<td>170.8 (80-9)</td>
<td>2.8 (0-2)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Kantorovich, 2000¹⁵</td>
<td>Obs.</td>
<td>USA</td>
<td>5</td>
<td>78</td>
<td>21.4/52.5</td>
<td>9.62 (2.5)</td>
<td>2.5 (0-2)</td>
<td>1.25 months</td>
</tr>
<tr>
<td>Grey, 2005¹⁶</td>
<td>Obs.</td>
<td>New Zealand</td>
<td>21</td>
<td>68.3</td>
<td>28/77</td>
<td>12.4 (7.1)</td>
<td>2.7 (0-1)</td>
<td>12 months</td>
</tr>
<tr>
<td>Grubbs, 2008¹⁷</td>
<td>Obs.</td>
<td>USA</td>
<td>112</td>
<td>58</td>
<td>45.9/79.1</td>
<td>15.7 (9.9)</td>
<td>2.7 (0-1)</td>
<td>Median duration</td>
</tr>
<tr>
<td>Isidro, 2009¹⁸</td>
<td>Obs.</td>
<td>Spain</td>
<td>27</td>
<td>67.5</td>
<td>28.7/77.1</td>
<td>16.6 (12.1)</td>
<td>2.7 (0-1)</td>
<td>12 months</td>
</tr>
<tr>
<td>Tucci, 2009¹⁹</td>
<td>Obs.</td>
<td>USA</td>
<td>56</td>
<td>63.6</td>
<td>36.4/94.5</td>
<td>13.1 (5.1)</td>
<td>2.7 (0-1)</td>
<td>34 weeks</td>
</tr>
<tr>
<td>Velayoudom-cephe, 2011²⁰</td>
<td>Obs.</td>
<td>France</td>
<td>22</td>
<td>66.8</td>
<td>28.1/39.5</td>
<td>17.2 (18.8)</td>
<td>2.7 (0-2)</td>
<td>6 months</td>
</tr>
<tr>
<td>Rathii, 2011²¹</td>
<td>Obs.</td>
<td>UK</td>
<td>23</td>
<td>59</td>
<td>14.8/75.8</td>
<td>21.9 (11-0)</td>
<td>NA</td>
<td>3 months</td>
</tr>
<tr>
<td>Shkolnik, 2010²²</td>
<td>Obs.</td>
<td>Israel</td>
<td>40</td>
<td>63</td>
<td>38.5/83</td>
<td>11.7 (3.6)</td>
<td>2.6 (0-1)</td>
<td>NA</td>
</tr>
<tr>
<td>Rao, 2012²²</td>
<td>Obs.</td>
<td>UK</td>
<td>28</td>
<td>69</td>
<td>32.2/136-4</td>
<td>13.7 (1.3)</td>
<td>2.6 (0-03)</td>
<td>18 ± 2 months</td>
</tr>
</tbody>
</table>

Obs., observational; NA, information not available.

*Mean age not available, data are in range.

**Duration and dose**

- 50 µg/day for 1 month
- 50,000 IU twice weekly for 5 weeks
- 50,000 IU/week for month and thereafter once a month for 12 months
- 50,000 IU/tab. Dose and duration as per directed by surgeons. Median cumulative dose: 400,000 IU
- 480–960 IU/day for 12 months
- 50,000 IU/week for 8 weeks followed by 800/day to 100,000 U/month
- 800–1,200 IU/day for 3 months or 100,000 U/month
- 20,000 IU per week for 12 weeks
- NA
- Variable dosage

Serum 25-OH Vitamin D

Serum Calcium

Serum PTH
Surgical Consult ➔ Localizing Studies

• Thyroid ultrasound
  – Right lobe 4.4 x 2.4 x 1.9 cm
  – Left lobe 4.3 x 2.1 x 1.6 cm
  – Isthmus 0.1cm
  – Right lobe is heterogeneous. No dominant nodules
  – Left lobe is heterogeneous. No dominant nodules.
  – No suspicious adenopathy. R level 3 lymph node visualized with a fatty hilum measuring 1.4 x 1.5 x 0.4 cm

• Impression: No evidence of a parathyroid adenoma visualized on this study.
Pre-op localization

• Imaging modalities:
  – Neck ultrasound (unrevealing 10-20% of cases)
  – Nuclear medicine scintigraphy parathyroid scan
  – CT scan

• Meta-analysis in 2012 investigated accuracy of these 3 techniques for pre-op localization

• 43 studies included: 19 ultrasound, 9 sestamibi-SPECT, 4 4D-CT

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>76.1%</td>
<td>93.2%</td>
</tr>
<tr>
<td>Sestamibi-SPECT</td>
<td>78.9%</td>
<td>90.7%</td>
</tr>
<tr>
<td>4D-CT</td>
<td>89.4%</td>
<td>93.5%</td>
</tr>
</tbody>
</table>

CT scan from admission...

- CT chest/abdomen/pelvis with contrast
  - Superior mediastinal soft tissue mass adjacent to esophagus. Etiology is unknown, may represent a primary nasopharyngeal mass, metastatic adenopathy, and/or less likely a diverticulum. Upper GI study may be helpful to exclude the possibility of small diverticulum
CT chest
NM parathyroid imaging with SPECT and CT anatomical localization

• 21.4 mCi Tc-99m sestamibi injected
• Early and delayed planar and early SPECT/CT images were acquired through portions of the neck and thorax
• On early SPECT, a focus of increased tracer uptake is localized in the retrotracheal area in the superior mediastinum, posterior to the lower pole of the right thyroid lobe.
• Impression: Concern for ectopic parathyroid adenoma in the retrotracheal superior mediastinum
NM parathyroid imaging with SPECT
Normal Parathyroid Development and Anatomy

Sources: UpToDate. Surgical Anatomy of the Parathyroid Glands
https://embryology.med.unsw.edu.au/embryology/index.php/Endocrine__Parathyroid_Development
Ectopic parathyroid adenoma

- Case series from 1978-2007 reported 252 patients with severe hypercalcemia due to hyperparathyroidism
  - 8% of adenomas were located ectopically
- Study in 2013 analyzed 1,562 patients who underwent surgery for primary hyperparathyroidism
  - 346 (22%) had ectopically located adenoma
  - Most common locations were thymus (38%), retroesophageal region (31%), intrathyroidal (18%)

Table 1 Location of 202 ectopic parathyroid glands and comparison of MIBI and US accuracy (p = 0.009)

<table>
<thead>
<tr>
<th>Location of ectopic glands</th>
<th>No. of ectopic glands</th>
<th>MIBI: no. correct (161/197) Overall sensitivity 89 %, PPV 90 %</th>
<th>US: no. correct (35/65) Overall sensitivity 59 %, PPV 90 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymus</td>
<td>77 (38 %)</td>
<td>61/74 (82 %)</td>
<td>11/23 (48 %)</td>
</tr>
<tr>
<td>Retroesophageal sites</td>
<td>62 (31 %)</td>
<td>54/61 (89 %)</td>
<td>11/19 (58 %)</td>
</tr>
<tr>
<td>Intrathyroidal sites</td>
<td>37 (18 %)</td>
<td>28/36 (78 %)</td>
<td>10/12 (83 %)</td>
</tr>
<tr>
<td>Mediastinal sites</td>
<td>13 (6 %)</td>
<td>11/13 (85 %)</td>
<td>0/2 (0 %)</td>
</tr>
<tr>
<td>Undescended</td>
<td>8 (4 %)</td>
<td>6/8 (75 %)</td>
<td>3/4 (75 %)</td>
</tr>
<tr>
<td>Carotid sheath</td>
<td>5 (3 %)</td>
<td>1/5 (20 %)</td>
<td>0/3 (0 %)</td>
</tr>
</tbody>
</table>

*MIBI* technetium-99m-sestamibi, US ultrasonography, PPV positive predictive value

Hospital course

• ENT discussed with family, surgical resection would have high morbidity. Defer surgery.
• IR unable to place G tube due to lack of safe window/hiatal hernia. Required continuous IVF for hydration
• For hypercalcemia, Pamidronate re-dosed 4 weeks after initial dose. Continued Cinacalcet at 90mg BID and vitamin D3 at 500IU daily.
Calcium trend

Discharged to NH... missed Endocrinology follow up
References