**Hypercalcemia**

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**Hypercalcemic Disorders**

- Primary Hyperparathyroidism*  
- Hypercalcemia of Malignancy  
- Granulomatous Disease  
- Vitamin D Intoxication  
- Vitamin A Intoxication  
- Hyperthyroidism  
- Thiazide Diuretics  
- Milk-Alkali Syndrome  
- Immobilization  
- Adrenal Insufficiency  
- Acute Renal Failure  
- Familial Hypocalciuric Hypercalcemia*

* ↑ PTH

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**Case History**

An 18 year old male presents for an 18 month history of swelling of the right side of the face and left hard palate.

**PE:** ENT: large firm right facial mass  
large firm left hard palate mass

**Lab:** Calcium 17.0 mg/dl  Phos 2.0 mg/dl  
Creatinine 0.5 mg/dl  Albumin 3.9 g/dl
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Lab: Calcium 17.0 mg/dl Phos 2.0 mg/dl
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What test will be most useful in the differential diagnosis of this patient’s hypercalcemia?
1. Serum protein electrophoresis
2. Complete blood count
3. Serum 25 OH Vitamin D
4. Serum PTH
5. Serum PTHrp

Case History

Repeat Labs:
Calcium 17.2 mg/dl (nl: 8.5-10.3)
PTH 108 pg/ml (nl: 10-65)

Biopsy of Right Maxillary Mass:
Brown Tumor of Hyperparathyroidism

Parathyroid Surgery:
2.0 x 1.5 cm Left Inferior Adenoma
Primary Hyperparathyroidism

Classification

- Adenoma 85%
- Hyperplasia 15%
- Carcinoma < 1%

Primary Hyperparathyroidism

Clinical Features

- Asymptomatic (> 50%)
- Arthritis
- Skeletal Disease
- Muscle Weakness
- Kidney Disease
- Band Keratopathy
- Gastrointestinal Disease
- Hypertension
- Psychiatric Disease
- Anemia

Hyperparathyroidism

Brown Tumor (Osteoclastoma)
Hyperparathyroidism
Osteitis Fibrosa Cystica

Hyperparathyroidism
Chondrocalcinosis

Hyperparathyroidism
Band Keratopathy
**Primary Hyperparathyroidism**

**Diagnosis**

- ↑ Serum Calcium
- ↓ Serum Phosphate
- ↑ Serum PTH (or high normal)

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What genetic syndrome is not associated with this disorder?
1. Familial Hyperparathyroidism
2. Multiple Endocrine Neoplasia Type 1
3. Multiple Endocrine Neoplasia Type 2A
4. Von Hippel Lindau Syndrome

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**Primary Hyperparathyroidism**

**Associations**

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>90%</td>
</tr>
<tr>
<td>Familial</td>
<td>10%</td>
</tr>
</tbody>
</table>

- Isolated Hyperparathyroidism
- Multiple Endocrine Neoplasia I
- Multiple Endocrine Neoplasia IIA
Multiple Endocrine Neoplasia I

- Pituitary Tumors
- Pancreatic Islet Tumors
- Parathyroid Hyperplasia

Germline Mutation: Menin Gene

Multiple Endocrine Neoplasia IIA

- Medullary Thyroid Carcinoma
- Pheochromocytoma
- Parathyroid Hyperplasia

Germline Mutation: Ret Gene (GDNF receptor)

Primary Hyperparathyroidism

Treatment

- Surgery
  - Adenoma - 1 gland
  - Hyperplasia - 3 1/2 glands
- Calcimimetic Drug* (CaSR Agonist)
- Bisphosphonates*

* Not FDA approved for this indication
Primary Hyperparathyroidism
Conditions Where Surgery is Recommended

- Serum Calcium > 1 mg/dl above normal
- Creatinine Clearance < 60 ml/min
- BMD T-Score ≤ -2.5 or Fragility Fracture
- Kidney Stones
- Age < 50 Years

Bilezikian J, J Clin Endo Metab 2009; 94:335-9

Case History
A 64 year old woman with hypercalcemia on routine screen.
Lab: Ca 10.6  Phos 3.1  PTH: 62 (nl: 10-65)
  Urine Ca 210 mg/24 hr. (nl, 100-300)
  BMD: Spine T-score -0.3  Hip T-score +0.5

Does she have primary hyperparathyroidism?
1. Yes
2. No
3. Insufficient information to know for sure

Case History
A 64 year old woman with hypercalcemia on routine screen.
Lab: Ca 10.6  Phos 3.1  PTH: 62 (nl: 10-65)
  Urine Ca 210 mg/24 hr. (nl, 100-300)
  BMD: Spine T-score -0.3  Hip T-score +0.5

What treatment do you recommend?
1. Observation with monitoring every 6-12 months
2. Parathyroid scan and surgery
3. Calcimimetic therapy (Cinacalcet) to lower PTH/Ca
4. Bisphosphonate therapy to prevent bone loss
5. Furosemide to promote renal calcium excretion
Primary Hyperparathyroidism
Non-Surgical Management Options

- Observation with Calcium/Vitamin D Rx
- Calcimimetic Drug – Cinacalcet (Sensipar)*
- Anti-Resorptive Drug – Bisphosphonate*

* Not FDA approved for this indication

Primary Hyperparathyroidism
Calcimimetic Therapy

RCT: 22 subjects with Primary Hyperparathyroidism
Cinacalcet or Placebo for 15 days

- Calcium (mg/dl)
- PTH (pg/ml)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Treatment (4 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>10.5</td>
<td>10.6</td>
<td>9.5</td>
<td>125</td>
</tr>
<tr>
<td>PTH</td>
<td>100</td>
<td>102</td>
<td>101</td>
<td>50</td>
</tr>
</tbody>
</table>

Placebo
Cinacalcet

Primary Hyperparathyroidism
Bisphosphonate Therapy

26 patients with HPTH (age: 67-81)
Alendronate vs. No Therapy x 2 years

32 patients with HPTH (mean age: 66)
Alendronate vs. No Therapy x 2 years

BMD Change (%) at 2 Years

Lumbar Spine
Total Hip
Femoral Neck

Rossini M, JBMR 2001; 16:113
Parker CR, JCEM 2002; 87:4482
Mild Asymptomatic
Primary Hyperparathyroidism
Monitoring Recommendations

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium</td>
<td>Every 6 Months</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>Every Year</td>
</tr>
<tr>
<td>Bone Density*</td>
<td>Every Year</td>
</tr>
</tbody>
</table>

*Spine, Hip and Mid-Radius

Bilezikian J, J Clin Endo Metab 2009; 94:335-9

Mild Asymptomatic
Primary Hyperparathyroidism
Management Recommendations

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>1,000-1,200 mg/day</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>400-600 Units/day</td>
</tr>
</tbody>
</table>

*Monitor serum calcium levels. If calcium increases significantly, consider surgery.

Bilezikian J, J Clin Endo Metab 2009; 94:335-9

Case History
A 61 year old woman with Type 2 DM, HTN, CRI.
PE: BP 145/85 Normal exam
Lab: Ca 8.8 Phos 5.7 Cr. 2.8 PTH 123 pg/ml (nl: 10-65)
25 Vitamin D 29 ng/ml (nl: 30-80)

What is the cause of the elevated serum PTH level?
1. Primary Hyperparathyroidism
2. Secondary Hyperparathyroidism due to renal failure
3. Secondary Hyperparathyroidism due to low vitamin D
4. Pseudohypoparathyroidism
5. Ectopic PTH production
Secondary Hyperparathyroidism

Calcium Deficiency
Vitamin D Deficiency

Renal Failure

Calcium Deficiency
Vitamin D Deficiency

Diffuse Hyperplasia

Diagnosis
PTH ↑
Serum Calcium ↓ / nl, OR
Serum Phosphorus ↑ / nl

Secondary Hyperparathyroidism

Treatment
- Correct Calcium and Vitamin D Deficiency
- Correct Hyperphosphatemia
- Suppress PTH Pharmacologically
  - Calcimimetic Drug – Cinacalcet (Sensipar)
  - Calcitriol Analog – Paracalcitol (Zemplar)
- Surgery: Subtotal Parathyroidectomy
### Secondary Hyperparathyroidism

**Calcimimetic Therapy**

RCT: 741 subjects with Secondary Hyperparathyroidism

Cinacalcet or Placebo for 26 weeks

<table>
<thead>
<tr>
<th>Calcium (mg/dl)</th>
<th>Placebo</th>
<th>Cinacalcet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Treatment</td>
<td>9.2</td>
<td>9.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PTH (pg/ml)</th>
<th>Baseline</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>642</td>
<td>643</td>
<td>693</td>
</tr>
</tbody>
</table>

Ca X Phos 4 15% with Cinacalcet

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### Case History

A 19 year old man complains of a 2-3 week history of weakness, nausea and vomiting.

PE: BP 90/65 P 108 Dehydration

Lab: Ca 19.1 Phos 3.9 CBC normal

PTH < 1 pg/ml (nl: 10-65)

What is the most likely cause of his hypercalcemia?

1. Hyperparathyroidism
2. Hypoparathyroidism
3. Hypercalcemia of malignancy
4. Vitamin D Toxicity
5. Sarcoidosis

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### Hypercalcemia of Malignancy

**Tumor Types**

- Lung Cancer (Squamous Cell)
- Breast Cancer
- Head and Neck Cancer
- Kidney Cancer
- Bladder Cancer
- Pancreatic Cancer
- Ovarian Cancer
- Multiple Myeloma
- Lymphoma
**Hypercalcemia of Malignancy**

**Mediators**
- PTH Related Peptide (PTH-RP)
- Transforming Growth Factors (TGF)
- Tumor Necrosis Factor (TNF)
- Interleukin 1, Interleukin 6
- Lymphotoxin
- Procathepsin D
- Prostaglandins
- 1,25 (OH)2 Vitamin D

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**Parathyroid Hormone Related Peptide**

**PTH-RP**

1 13 141

**PTH**

1 13 84

Binds to PTH Receptor

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**Hypercalcemia of Malignancy**

**Diagnosis**

- ↑ Serum Calcium
- ↓ Serum PTH
- ↑ Serum PTH-RP

(or other mediator)
Hypercalcemia of Malignancy

Treatment

Promote Urine Calcium Excretion
- Saline infusion

Inhibit Bone Resorption
- Bisphosphonates
- Calcitonin
- Plicamycin

Remove Calcium
- Dialysis

Case History

A 32 year old woman presents for an insurance examination.
FH: mother and sister have elevated calcium
Lab: Calcium 11.0 Phos 4.1  PTH: 67 pg/ml (nl: 10-65)
Urine Ca 32 mg/24 hr. (nl: 100-300)
Ca/Creat Clearance Ratio: 0.005
What is the most appropriate management strategy?
1. Removal of solitary parathyroid adenoma
2. Removal of 3 and ½ hyperplastic parathyroid glands
3. Search for a cause of malignancy
4. No treatment is needed
5. Reduce calcium and vitamin D intake

Calcium Sensor Receptor

Parathyroid cell - PTH secretion
Parafollicular C-cell - Calcitonin secretion
Renal tubular cell - Calcium excretion
Calcium Sensor Receptor

Parathyroid cell - ↑ PTH secretion

Renal tubular cell - ↓ Calcium excretion

Familial Hypocalciuric Hypercalcemia

Diagnosis

- Family History
- ↑ Serum Calcium (mild)
- ↑ Serum PTH (mild)
- ↓ Urinary Calcium
  - urine calcium / creatinine clearance ratio
  - \( \frac{Uca \times Pcr}{Pca \times Ucr} < .01 \)

Familial Hypocalciuric Hypercalcemia

Treatment

- No Treatment Necessary
- Avoid Surgery
Case History
A 40 year old woman has hypercalcemia on annual exam.
Meds: Multivitamin and supplements
PE: BP 120/84 Normal otherwise
Lab: Ca 11.1 mg/dl Phos: 5.1 mg/dl
   PTH < 1 pg/ml 25 Vitamin D 152 ng/ml (nl: 30-80)
What test is most likely to yield the correct diagnosis?
1. Chest x-ray
2. Serum protein electrophoresis
3. 24 hour urinary calcium and creatinine
4. PTHrp level
5. 25 OH Vitamin D level

Vitamin D Toxicity with Hypercalcemia

Mechanism
Excess Vitamin D stimulates increased
GI Calcium and Phosphorus absorption

Treatment
Discontinue Vitamin D intake until
Calcium and 25 OH Vitamin D nl
Hydration
Loop diuretic

Thank you