Medical Evaluation and Imaging Approach to Parathyroid Disease

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Learning Objectives

• Epidemiology of primary hyperparathyroidism (PHPT)
• Diagnosis of PHPT
• Indications for parathyroidectomy
• Review imaging modalities for parathyroid gland assessment
• Fundamentals of parathyroid ultrasound
Epidemiology of PHPT

• Prevalence in U.S. ~ 1 in 1000
• F:M ~2-3:1
• Mean age at diagnosis: 55 years
• Glands involved:
  – 75-80% single adenoma
  – 10% multiple adenomas (more common in older pts)
  – 10-15% four gland hyperplasia
  – 1% parathyroid carcinoma
• 95% sporadic; others associated with genetic syndromes:
  – Multiple endocrine neoplasia type 1 or 2a
  – Familial hyperparathyroidism/Jaw-tumor syndrome
  – Familial isolated hyperparathyroidism
Familial Hypocalciuric Hypercalcemia

• May biochemically mimic PHPT
• These patients should not have surgery!
• Autosomal dominant inactivating mutation of Ca Sensing Receptor
• Distinguish HPT from FHH by calcium/creatinine clearance ratio (24-hour urine collection)
  – FHH suggested by ratio < 0.01
  – PHPT suggested by ratio > 0.01-0.02

\[
\frac{\text{CaCl}}{\text{CrCl}} = \frac{\text{UCa} \times \text{sCr}}{\text{UCr} \times \text{sCa}}
\]
# Biochemical Diagnosis of Hyperparathyroidism

<table>
<thead>
<tr>
<th></th>
<th>$\text{Ca}^{2+}$</th>
<th>$\text{PO}_4$</th>
<th>$\text{PTH}$</th>
<th>$1, 25$-$\text{D}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary HPT</strong></td>
<td>↑</td>
<td>↓</td>
<td>↑ (or high normal)</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Secondary HPT</strong></td>
<td>↓</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
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<tr>
<td><strong>Tertiary HPT</strong></td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
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Asymptomatic PHPT Indications for Surgery - 2014 Revision

<table>
<thead>
<tr>
<th>Feature</th>
<th>2008</th>
<th>2014</th>
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<tbody>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Serum Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>1.0 mg/dL &gt; ULN</td>
<td>1.0 mg/dL &gt; ULN</td>
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<tr>
<td>Renal</td>
<td>eGFR &lt; 60 cc/mL</td>
<td>Cr Clearance &lt; 60 cc/mL OR 24-hr urine calcium &gt; 400 mg/day &amp; ↑ stone risk by biochemical analysis OR imaging evidence of nephrolithiasis/nephrocalcinosis</td>
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<tr>
<td>Skeletal</td>
<td>Osteoporosis: DXA T-score &lt;-2.5 at any site or fragility fracture</td>
<td>Osteoporosis: DXA T-score &lt;-2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius OR imaging evidence of vertebral fracture</td>
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Classically bone involvement in PHPT affects cortical > trabecular bone

Requires 3-site DXA! Distal 1/3 forearm is most sensitive site
Parathyroid Imaging
75-80% Usual Location: ~1cm above the inferior thyroid artery

15% Upper Location: near upper pole of thyroid

~ 5% Ectopic
50-65% Usual Location: ~1cm below the inferior thyroid artery

15-20% Near Location: Just above or below usual location

25-35% level VII, thoracic inlet or upper mediastinum

INFERIOR PARATHYROID GLANDS
Pre-operative Localization

• Pre-operative localization allows for more limited surgery (minimally invasive parathyroidectomy vs. bilateral neck exploration)

• Most common modalities:
  – High resolution neck ultrasound
  – Nuclear medicine technetium-99 sestamibi +/- SPECT
  – SPECT-CT fusion

• Other modalities:
  – 4D CT, neck MRI, PET
Technetium-99 sestamibi

- $^{99m}$Tc-sestamibi taken up by mitochondria in thyroid and parathyroid; radiotracer has longer retention in mitochondria-rich parathyroid cell
  - Images 2 hours post-injection show retained tracer activity from hyperfunctioning adenoma
  - Limited anatomical detail

- Can combine with single proton emission computed tomography (SPECT) – 3D sestamibi scan; improved anatomic detail, better localization of ectopic glands
Parathyroid Imaging: 99mTc Sestamibi

- **Advantages**
  - PPV 90-100% for solitary adenomas
  - May detect ectopic glands
- **Disadvantages**
  - Less accurate for double adenomas or hyperplasia
  - Ionizing radiation
  - Cost
  - Concurrent thyroid pathology (Hurthle cell lesions, chronic lymphocytic thyroiditis)
Detection of Primary Hyperparathyroidism: US and Sestamibi

US and sestamibi combined:
>90% sensitivity for single adenoma\(^2\)
60% for double adenoma\(^3\)

\(^1\)Ruda, Otolaryngol Head Neck Surg 2005; \(^2\)De Feo, Radiology 2000; \(^3\)Haciylani J Am Coll Surg 2003
$^{99}$Tc-sestamibi SPECT

- Sensitivity for single adenoma 92-98% vs. 71-79% for planar sestamibi
- ~83% detection of double adenoma (vs. ~30% planar)
- ~45% detection of multiglandular hyperplasia (similar)
- Useful for localization of ectopic parathyroid adenomas
SPECT with CT Fusion

- Combines SPECT with CT to better discriminate adenomas from other anatomic landmarks
- Advantage in anatomic localization of ectopic parathyroid glands (46% vs. 13% SPECT alone)

*Wimmer Arch Surg 2010*
Parathyroid Ultrasound

• Technique
  – High frequency probe ≥10MHz with Doppler
  – Hyperextend patient’s neck
  – Angle into mediastinum
  – Compression (parathyroid doesn’t compress)

• Advantages
  – Cost
  – No radiation exposure
  – Evaluates thyroid (20-30% of pts with concomitant thyroid pathology)

• Disadvantages
  – Operator dependent
  – Does not identify ectopic glands
Transverse Parathyroid Ultrasound

Anterior

Vessels

thyroid

parathyroid

Trachea

Posterior
Transverse Parathyroid Ultrasound

Anterior

thyroid

trachea

Posterior

parathyroid
Sagittal Parathyroid Ultrasound

Superior

thyroid

superior parathyroid

Inferior

inferior parathyroid
Sagittal Parathyroid Ultrasound

Superior Parathyroid

Inferior Parathyroid

thyroid

superior parathyroid
What Does a Parathyroid Adenoma Look Like?

Many shapes – most common are oval-round
Well-defined margins
Homogeneous echotexture, hypoechoic
Typical Parathyroid Adenoma

Transverse

Sagittal
Parathyroid Vascularity
Parathyroid Vascularity

- Polar vascular pattern (60-70%)
- Diffuse, complex vascular pattern (15-20%)
- Scant vascular pattern (15-20%)
Polar Vascular Pattern

Sagittal
Diffuse Vascular Pattern

Longitudinal
Scant Vascular Pattern

Transverse
Parathyroid Cyst

• Very rare
• More common in women
• 65% of cases involve an inferior parathyroid gland
• 95% of cases are located below the inferior margin of the thyroid lobe
• Incidental finding, not associated with hyperparathyroidism!
Parathyroid Cyst

Calcium=9.4 mg/dL (8.5-10.5), iPTH=2.9 pmol/L (1.6-6.9)
Parathyroid or Metastatic Lymph Node in Differentiated Thyroid Cancer?

- Parathyroid adenoma vs. metastatic LN:
  - Non-calcified
  - Visualization of polar vessel with peripheral rim flow vs a central arterial supply
  - Less likely to have cystic change
  - FNA with washout for PTH and thyroglobulin may been needed for clarification

Kobaly, Mandel, Langer JCEM 2014
53 yo woman with iPTH of 27.5 pmol/L (1.6-6.9) and Ca 12.4 mg/dL
Tumor was invasive into the nerve and soft tissue

US features of parathyroid carcinoma:
- Large (mean 2.5 cm)
- Hypoechoic but heterogeneous
- Lobulated borders
- Elliptical shape

Keys to Parathyroid Ultrasound

• Appearance
  – Oval, homogeneous, hypoechoic

• Location
  – Superior: posterior to the mid portion of thyroid
  – Inferior: inferior to the lower pole of thyroid

• Vascularity
  – Polar vascularity

• Experience
Thank You!
# Recommended Monitoring During Non-Operative Management of PHPT

<table>
<thead>
<tr>
<th>Measurement</th>
<th>2014 Monitoring Guidelines</th>
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<tr>
<td>Serum calcium</td>
<td>Annually</td>
</tr>
<tr>
<td>Serum creatinine/eGFR</td>
<td>Annually +/- stone profile/imaging if kidney stones suspected</td>
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<tr>
<td>Bone density</td>
<td>Every 1-2 years (3 sites) +/- vertebral imaging if clinically indicated (back pain, height loss)</td>
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</tbody>
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Bilezikian et al, JCEM 2014
4D CT Scanning

- Parathyroid adenomas have rapid uptake/washout of contrast that helps with anatomic localization
- Useful in re-operative settings when other imaging is negative
- 88% sensitivity for abnormal parathyroid gland compared to 54% (SPECT) and 21% (ultrasound) in re-operative setting
- 50-fold higher radiation exposure to thyroid than sestamibi
Non-Surgical Management of PHPT

• Adequate calcium (1000 mg/day) and vitamin D intake, avoid calcium supplements
• Maintain adequate hydration
• Pharmacotherapy for osteoporosis
• Weight bearing exercises

• Calcimimetics: Calcium-sensing receptor agonist
  – Cinacalcet (Sensipar): FDA approved for PHPT with:
    – **Severe** hypercalcemia and contraindication to parathyroidectomy
    – Parathyroid carcinoma
What About “Normocalcemic” PHPT?

- Normal serum/ionized $\text{Ca}^{2+}$, ↑ PTH, no other secondary causes of HPT
- Surgery may be considered with kidney stones, nephrocalcinosis, fracture/worsening BMD

Bilezikian et al., 2014
Minimally Invasive Parathyroidectomy

• Unilateral targeted excision of parathyroid adenoma with intraoperative PTH monitoring

• Benefits
  – Shorter surgery time
  – Smaller incisions
  – Fewer complications
    • Post-op hypocalcemia

• Disadvantages
  – Requires accurate preoperative localization of parathyroid adenoma
  – May miss multiglandular disease
Ultrasound-Guided Parathyroid FNA

- Cytology:
  - 30-50% nondiagnostic

- PTH level:
  - measure in needle washout
  - Very high in parathyroid tissue

- FNA-PTH >101pg/ml had 100% sensitivity and specificity for verification of parathyroid tissue