An Approach to Hypercalcemia

Endocrine GP Symposium
23rd July 2016
Dr. Daphne Lee
Issues Pertinent to Primary Care?

• What the clinical features of hypercalcemia?
• How should I investigate?
• When should I refer urgently?
• When should I refer to Endocrine?
Terminologies

• What is:
  – Total Calcium?
  – Ionized Calcium?
  – Adjusted Calcium?
Distribution of Calcium in the Body

- **Hydroxyapatite**
  - 98.9%
  - = 31 mol
  - = 1250g
  - 1% of which is available as an exchangeable pool

- **1% of total body calcium is present in the cells**

- **0.1% of total body calcium is in the extracellular fluid**:
  - **Ionised Calcium: Ca**++
    - 50%
    - 1.2 mmol/L
  - **Protein-bound Calcium**
    - 41%
    - 1.2 mmol/L
  - **Anion-bound calcium**
    - 9%, 0.2 mmol/L

- **Present as free, active cation**
- **Diffuses easily across capillary membranes**
- **Bound mainly to albumin**
- **Cannot diffuse across capillary membranes**
- **Bound to small anionic molecules, e.g. phosphate and citrate**
- **Diffuses easily across capillary membranes**

*Guyton & Hall Textbook of Medical physiology, 14th ed. E. Hall; Chapter 79*
Measuring Calcium

• **Total Calcium =**
  – Ionized calcium + protein bound calcium + anion bound calcium

• **Corrected (adjusted) Calcium =**
  – Hypoalbuminemia affects protein bound calcium
  – Corrected calcium = what total calcium would be if patient had normal albumin level
  – *Measured total calcium (mmol/L) + 0.02 (40-serum albumin in g/L)*
Measuring Calcium (cont’d)

• Ionized Calcium =
  – Fraction that is under homeostatic control
  – Affected by changes in pH
    • Alkalosis increases calcium binding to protein; decreases ionized fraction
    • Acidosis decreases calcium binding; increases ionized fraction
  – Possible indications:
    • Critical illness
    • Chronic liver or kidney disease
    • Patients receiving citrated blood
    • Caveat: problems with accuracy of assay, lack of standardization
Biological Importance of Calcium

• Crucial regulator of various cellular events:
  – Muscle contraction
  – Cell signaling
  – Hormone secretion
  – Neuromuscular transmission
  – Co-factor for many steps involved in coagulation
Calcium Regulation

- Key players:
  - 3 Regulators:
    - Parathyroid hormone (PTH)
    - Vitamin D
    - Calcitonin
  - 4 Organs:
    - Parathyroid glands
    - Bone
    - Kidneys
    - Gut
Parathyroid Hormone (PTH): Retains Calcium in the Circulation

- **Actions of PTH:**
  - Increases bone resorption
  - Increases calcium reabsorption at DCT
  - Decreases phosphate reabsorption
  - Increases activation of 1,25 OH Vit D
    - Increases calcium and phosphate absorption from intestine
Vitamin D

- Actions of Vitamin D:
  - Increases calcium and phosphate absorption in gut
  - Increases bone resorption when calcium levels are low
  - Increases calcium and phosphate reabsorption in the kidneys
“Bones, Stones, Psychic Moans”

- **Bones:**
  - Bone pain
  - Pseudogout
  - Chondrocalcinosis
  - Osteoporosis

- **Stones (Renal):**
  - Polyuria
  - Nephrogenic DI
  - Nephrolithiasis
  - Renal impairment

- **Psychic Moans (Psychiatric):**
  - Anxiety
  - Depression
  - Cognitive dysfunction
  - Psychosis

- **Cardiovascular:**
  - Hypertension
  - Arrhythmias
  - Short QTc
  - Calcification of valves, coronary arteries

- **GIT:**
  - Constipation
  - Anorexia
  - Nausea vomiting
  - Pancreatitis

- **Neurological**
  - Hypotonia
  - Hyporeflexia
  - Myopathy
  - Paresis
Clinical Features of Hypercalcemia

• Symptoms can be non specific
• Related to severity and rate of change of serum calcium
• Symptoms of underlying diseases causing hypercalcemia may dominate the clinical picture
Asymptomatic, non-specific symptoms

Coma, confusion, psychosis, arrhythmias

Polyuria, polydipsia, anorexia, changes in sensorium

Hypercalcemic crisis

Spectrum of Hypercalcemia

Total serum calcium level, mg/dL (mmol/L)

8 (2) 10 (2.5) 12 (3) 14 (3.5) 16 (4)

Ionized serum calcium level, mg/dL (mmol/L)

4 (1) 5.6 (1.4) 8 (2) 10 (2.5) 12 (3)

FIGURE 1. Spectrum of hypercalcemia indicated by serum total and ionized calcium levels.
Case Vignettes: Madam SAK

• 69 year old Chinese lady

• Past medical history of:
  – Hypertension
  – Hyperlipidemia
  – ?Cognitive impairment
    • Referred to GRM for STML and delirium after fall
    • Noted serum Calcium (adjusted) 2.78 mmol/L

What would you like to do now?
1. Enquire regarding symptoms of hypercalcemia
2. Drug history especially thiazides
3. Ask for symptoms of underlying malignancy
4. Repeat calcium with PTH, phosphate
5. Review old results for previous calcium levels
6. Look for end-organ involvement (renal, osteoporosis)
Madam SAK

- Polyuria, constipation
- Mood disturbances, irritability
- No thiazides, lithium, antacids, calcium or vitamin D supplements
- No breast lumps, no chronic cough, no symptoms of anemia, back pain
- Normal physical examination
- Post fall (non traumatic) had right distal radial ulnar fracture
Madam SAK

• Corrected Calcium 3.10 mmol/L (2.15-2.50)
• Phosphate 0.70 mmol/L (0.85-1.45)
• PTH 15.6 pmol/L (1.6-6.9)
• Vitamin D 17.4 ug/L (30-100)
• Creatinine 38 umol/L (45-84)
• FBC normal
• LFT normal

• Differentials?
Madam SAK

• XR Lumbar spine: anterior wedging of L1 vertebra

• Bone Mineral Density
  – NOF: 0.392 g/cm³, T score -3.9, Z score -2.1
  – Hip: 0.510 g/cm³, T score -3.5, Z score -1.9
  – Total Spine: 0.633 g/cm³, T score -3.2, Z score -1.2
  – Wrist: 0.429 g/cm³, T score -4.4, Z score -2.5
Inverse Relationship Between Calcium and Parathyroid Hormone (PTH)
<table>
<thead>
<tr>
<th>Causes of Hypercalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parathyroid hormone-related</strong></td>
</tr>
<tr>
<td>Sporadic, familial, associated with multiple endocrine neoplasia I or II</td>
</tr>
<tr>
<td>Tertiary hyperparathyroidism</td>
</tr>
<tr>
<td>Associated with chronic renal failure or vitamin D deficiency</td>
</tr>
<tr>
<td><strong>Primary hyperparathyroidism</strong></td>
</tr>
<tr>
<td><strong>Vitamin D-related</strong></td>
</tr>
<tr>
<td>Vitamin D intoxication</td>
</tr>
<tr>
<td>Usually 25-hydroxyvitamin D₂ in over-the-counter supplements</td>
</tr>
<tr>
<td>Granulomatous disease sarcoidosis, berylliosis, tuberculosis</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
</tr>
<tr>
<td>Humoral hypercalcemia of malignancy* (mediated by PTHrP)</td>
</tr>
<tr>
<td>Solid tumors, especially lung, head, and neck squamous cancers, renal cell tumors</td>
</tr>
<tr>
<td>Local osteolysis* (mediated by cytokines) multiple myeloma, breast cancer</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td>Thiazide diuretics (usually mild)*</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Milk-alkali syndrome (from calcium antacids)</td>
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<tr>
<td>Vitamin A intoxication (including analogs used to treat acne)</td>
</tr>
<tr>
<td><strong>Other endocrine disorders</strong></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Acromegaly</td>
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<tr>
<td>Pheochromocytoma</td>
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<tr>
<td><strong>Genetic disorders</strong></td>
</tr>
<tr>
<td>Familial hypocalciuric hypercalcemia: mutated calcium-sensing receptor</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Immobilization, with high bone turnover (e.g., Paget’s disease, bedridden child)</td>
</tr>
<tr>
<td>Recovery phase of rhabdomyolysis</td>
</tr>
</tbody>
</table>
Primary Hyperparathyroidism

- Parathyroid glands were the last major organ to be recognized in humans
  - First described by Ivar Sandstrom in 1879

- First parathyroidectomy performed for HPT in Vienna in 1925 by Dr. Felix Mandl

- Primary hyperparathyroidism was first diagnosed in the US in 1926 by Dr. Eugene DuBois
Primary Hyperparathyroidism

- Excessive secretion of parathyroid hormone (PTH) by parathyroid glands
- Classical disease is characterized by:
  - Symptomatic hypercalcemia
  - Renal calculi
  - Bone disease: Osteitis fibrosa cystica, brown tumors, osteoporosis
- May present with parathyroid crisis
Evolution of the Clinical Presentation of Primary Hyperparathyroidism

• Development of the multichannel autoanalyser in the 1970s allowed calcium levels to be routinely available
• Increasingly sophisticated PTH immunoassays
  – First PTH immunoassay was developed by Berson and Yalow in the 1960s
• Increasing incidence of asymptomatic hyperparathyroidism
  – Robert Coffey reported increased incidence of asymptomatic HPT from 5% (pre-1970) to 40% (post 1970)
  – Mayo Clinic reported 64% of their cases of HPT during 1974-1980 were asymptomatic
Causes of Primary Hyperparathyroidism

• Occurs at any age; majority are above age of 50
• Single gland adenoma is the most common cause (75-85%)
• Multi-gland disease (10-15%)
  – Usually in the context of familial diseases e.g. MEN 1, 2a
• Parathyroid carcinoma (~1%)
Surgical Management of Primary Hyperparathyroidism

• Gold standard of management is parathyroid surgery

• Unilateral parathyroidectomy vs. bilateral neck exploration
  – Role of pre-op localisation studies and intra-op PTH monitoring
  – Bilateral approach is still indicated for those with familial disease
<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>2002</th>
<th>2008</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<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>
<td>1.0 mg/dL (0.25 mmol/L)</td>
<td>1.0 mg/dL (0.25 mmol/L)</td>
</tr>
<tr>
<td>Skeletal</td>
<td>BMD by DXA: Z-score &lt; −2.0 (site unspecified)</td>
<td>BMD by DXA: T-score &lt; −2.5 at any site</td>
<td>BMD by DXA: T-score &lt; −2.5 at any site</td>
<td>A. BMD by DXA: T-score &lt; −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B. Vertebral fracture by x-ray, CT, MRI, or VFA</td>
</tr>
<tr>
<td>Renal</td>
<td>A. eGFR reduced by &gt;30% from expected</td>
<td>A. eGFR reduced by &gt;30% from expected</td>
<td>A. eGFR &lt; 60 cc/min</td>
<td>A. eGFR &lt; 60 cc/min</td>
</tr>
<tr>
<td></td>
<td>B. 24-h urine for calcium &gt;400 mg/d (&gt;10 mmol/d)</td>
<td>B. 24-h urine for calcium &gt;400 mg/d (&gt;10 mmol/d)</td>
<td>B. 24-h urine for calcium &gt;400 mg/d (&gt;10 mmol/d) and increased stone risk by biochemical stone risk analysis</td>
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</tr>
<tr>
<td>Age, y</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
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</table>

Abbreviations: eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging. Patients need to meet only one of these criteria to be advised to have parathyroid surgery. They do not have to meet more than one.

Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible and in patients opting for surgery, in the absence of meeting any guidelines, as long as there are no medical contraindications.
Medical Management

• General Measures
  – Ensure good hydration
  – Avoid thiazide diuretics
  – Encourage ambulation
  – Avoid excessive calcium intake
  – Modest replacement of vitamin D 800-1000IU/day

• Pharmacologic agents
  – Bisphosphonates for symptomatic hypercalcemia/osteoporosis
  – CaSR modulators e.g. cinacalcet to control calcium levels
Familial Hypocalciuric Hypercalcemia (FHH)

- Autosomal-dominant condition
- Caused by mutation in the calcium sensing receptor gene
- Patients have moderate hypercalcemia from an early age with relatively low urinary calcium excretion
- PTH levels can be normal or mildly elevated
- Differentiated from HPTH by calcium creatinine clearance of <0.01
- Parathyroidectomy is not beneficial
- Moderate size focus of moderate to intensely increased tracer uptake in the region of the upper pole of left lobe of thyroid, compatible with a left superior parathyroid adenoma
Madam SAK

- Underwent left upper parathyroidectomy
  - Intraop: baseline PTH 23.9 pmol/L -> 15 minute post excision 5.5 pmol/L
  - Histology:
    - 2x1.5x0.9cm specimen weighing 1.57g
    - Hyperplastic parathyroid gland with attenuated capsule in keeping with parathyroid adenoma. No evidence of malignancy.

- Post op follow up:
  - Calcium 2.27 mmol/L
  - Phospate 1.16 mmol/L
  - PTH 5.4 pmol/L
Case Vignette: Mr. TAC

• 73 year old Chinese man

• Past medical history:
  – Stage 4 diffuse large b cell lymphoma defaulted follow up for 1 year
  – DM
  – Hypertension
  – Hyperlipidemia
  – CKD, baseline Cr 110
  – IHD
Mr. TAC

- Admitted for one month history of vomiting, weakness, lethargy and functional decline
- On day of admission, noted to be confused and drowsy
- On clinical examination, GCS 10, dehydrated
Mr. TAC

- Creatinine 370 umol/L (59-104)
- Urea 26.3 mmol/L (2.8-7.6)
- Ca, adjusted 4.11 mmol/L (2.15-2.50)
- Phosphate 1.52 mmol/L (0.85-1.45)
- PTH 1.0 pmol/L (1.6-6.9)
- Vitamin D 17.8 ug/L (30-100)
Hypercalcemic Crisis

• MEDICAL EMERGENCY
• Ca usually >4.0 mmol/L
• Primary symptoms include oliguria/anuria and mental state changes (including somnolence and eventually coma)
• Majority of cases are due to primary hyperparathyroidism and malignancy
• Priority is to stabilize the patient
• Hydration, hydration, hydration
• Refer to nearest ED as soon as possible

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mode of action</th>
<th>Onset of action</th>
<th>Duration of action</th>
</tr>
</thead>
</table>
| Isotonic saline hydration | Restoration of intravascular volume  
                          Increases urinary calcium excretion                      | Hours           | During infusion    |
| Calcitonin         | Inhibits bone resorption via interference with osteoclast function  
                          Promotes urinary calcium excretion                          | 4 to 6 hours    | 48 hours           |
| Bisphosphonates    | Inhibit bone resorption via interference with osteoclast recruitment and function | 24 to 72 hours  | 2 to 4 weeks       |
| Loop diuretics*    | Increase urinary calcium excretion via inhibition of calcium reabsorption in the loop of Henle | Hours           | During therapy     |
| Glucocorticoids    | Decrease intestinal calcium absorption  
                          Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in patients with granulomatous diseases or lymphoma | 2 to 5 days     | Days to weeks      |
| Denosumab          | Inhibits bone resorption via inhibition of RANKL                             | 4 to 10 days    | 4 to 15 weeks      |
| Calcimimetics      | Calcium sensing receptor agonist, reduces PTH (parathyroid carcinoma, secondary hyperparathyroidism in CKD) | 2 to 3 days     | During therapy     |
| Dialysis           | Low or no calcium dialysate                                                  | Hours           | During treatment   |

* Loop diuretics should not be used routinely. However, in patients with renal insufficiency or heart failure, judicious use of loop diuretics may be required to prevent fluid overload during saline hydration.

Hypercalcemia of Malignancy

- Occurs in 20-30% of patients with cancers
- Malignancy is usually evident clinically by the time it causes hypercalcemia
- Often denotes poor prognosis

### Malignancies associated with hypercalcemia

<table>
<thead>
<tr>
<th>Humoral hypercalcemia (PTHrP):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinomas</td>
</tr>
<tr>
<td>Renal carcinomas</td>
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<tr>
<td>Bladder carcinoma</td>
</tr>
<tr>
<td>Breast cancer</td>
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<tr>
<td>Ovarian carcinoma</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>CML</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td><strong>Osteolytic metastases:</strong></td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td><strong>1,25-dihydroxyvitamin D:</strong></td>
</tr>
<tr>
<td>Lymphoma (non-Hodgkin, Hodgkin, lymphomatosis/granulomatosis)</td>
</tr>
<tr>
<td>Ovarian dysgeminomas</td>
</tr>
<tr>
<td><strong>Ectopic PTH secretion:</strong></td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
</tr>
<tr>
<td>Lung carcinomas</td>
</tr>
<tr>
<td>Neuroectodermal tumor</td>
</tr>
<tr>
<td>Thyroid papillary carcinoma</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
</tr>
</tbody>
</table>

CML: chronic myeloid leukemia; PTH: parathyroid hormone; PTHrP: parathyroid hormone-related protein.
Mechanisms Causing Hypercalcemia of Malignancy

- **PTHrP**: Bone calcium release. Frequency: 80%. Tumor types: Breast, lung, NHL.
- **PTH**: Bone calcium release. Frequency: Rare case reports.
- **1,25(OH)₂D**: Intestinal calcium absorption. Frequency: <1%. Tumor types: Lymphomas.
- **Osteolysis**: Bone calcium release. Frequency: 20%. Tumor types: Breast, lung, myeloma.
Miscellaneous Causes of Hypercalcemia

- **Drugs**
  - Thiazides: lower urinary calcium excretion, can unmask hypercalcemia in a patient with underlying hyperparathyroidism
  - Lithium: exact mechanism unknown
    - increase in the set point at which calcium suppresses PTH release, leads to increased secretion of PTH and mild hypercalcemia
    - Significant association with multigland disease
    - Cessation of therapy may not correct the hypercalcemia/hyperparathyroidism

- **Milk alkali syndrome**
  - Occurs in the setting of high intake of milk or calcium carbonate coupled with absorbable alkali
  - More common when absorbable antacids were standard treatment for peptic ulcer disease

- **Prolonged immobilisation**
  - Due to increased bone resorption
Endocrine Causes of Hypercalcemia

• Hyperthyroidism
  – Mild hypercalcemia occurs in 15-20% of thyroxic patients
  – Due to thyroid hormone mediated increase in bone resorption

• Adrenal Insufficiency
  – Multifactorial including increased bone resorption, volume contraction, hemoconcentration, increased c calcium reabsorption

• Phaeochromocytoma
  – Usually due to concurrent hyperparathyroidism in the context of MEN 2
  – Phaeochromocytomas can also secrete PTHrp
Suggested Approach

• Review history:
  – Classical presentation very rare
  – Subtle manifestations more common
• Look for associated conditions/complications
• Review medications
• Pursue symptoms of underlying malignancy
Suggested Approach

• Physical examination
  – General well being: hydration status, mental state
  – Band keratopathy (rare)
  – Features of malignancy e.g. breast lump
  – Kyphosis, bone tenderness
Suggested Approach

• Patient who is unwell and severe hypercalcemia should be referred to ED immediately
• Patients with mild hypercalcemia (Ca <3.0):
  – Ensure adequate fluid intake of 3 to 4 L per day if not contraindicated
  – Encouraging mobility
  – Cautious use or elimination of drugs that may complicate management
  – Patient and family education on symptoms of severe hypercalcemia and when to go to ED
Diagnostic approach to hypercalcemia

Elevated serum calcium
  ↓
  Check repeat
  (Total calcium corrected for albumin or ionized calcium)

Hypercalcemia confirmed
  ↓
  Clinical evaluation
  ↓
  Measure intact PTH

Elevated
  ↓
  Primary hyperparathyroidism

Mid-upper or minimally elevated *
  ↓
  Primary hyperparathyroidism, consider FHH ¶

Low (<20 pg/mL)
  ↓
  Consistent with non-PTH mediated hypercalcemia
  ↓
  Measure PTHrp and vitamin D metabolites

PTHrp elevated
  ↓
  Scan for malignancy

Elevated 1,25D
  ↓
  Chest x-ray (lymphoma, sarcoid)

Normal vit D
  ↓
  Normal PTHrp

Elevated 25D
  ↓
  Consider other causes
  Measure SPEP, UPEP, TSH, vitamin A

Check medications, vitamins, herbal supplements

PTH: parathyroid hormone; FHH: familial hypocaliuric hypercalcemia; PTHrp: parathyroid hormone-related peptide; 1,25D: 1,25-dihydroxyvitamin D; 25D: 25-hydroxyvitamin D; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis; TSH: thyroid stimulating hormone.

* Serum PTH ranging from 35 to 65 pg/mL in an assay whose normal range is 10 to 60 pg/mL.

¶ Refer to UpToDate topics on primary hyperparathyroidism and familial hypocaliuric hypercalcemia for details.
HYPERCALCEMIA

Measure serum total and ionized calcium

Normal

Hemoconcentration or serum protein abnormality

Elevated

Clinical evaluation
History, physical examination
Measure electrolytes, BUN, creatinine, phosphate, alkaline phosphatase

Measure serum PTH

Normal or high

PTH-dependent hypercalcemia
Proceed to algorithm for diagnosis of PTH-dependent hypercalcemia (see Fig. 26–31)

Low

PTH-independent hypercalcemia
Evaluate for other causes of PTH-independent hypercalcemia (see Table 26–2)

Search for occult malignancy
Chest radiograph
Serum/urine IEP
Mammogram
Abdominal/chest CT

No

Yes

Malignancy-associated hypercalcemia
Select appropriate therapy for malignancy; consider bisphosphonate
• What the symptoms and signs of hypercalcemia?
• How should I investigate?
• When should I refer urgently?
• When should I refer to Endocrine?
THE END
<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum Ca²⁺</th>
<th>Serum P</th>
<th>Serum PTH</th>
<th>Serum 25(OH)D</th>
<th>Serum 1,25(OH)₂D</th>
<th>Associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td>↑</td>
<td>N or ↓</td>
<td>High N</td>
<td>N</td>
<td>N</td>
<td>80% Asymptomatic nephrolithiasis, osteoporosis, hypercalcemic sx</td>
</tr>
<tr>
<td>Cancer with extensive bone metastases</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>or N</td>
<td>History of primary tumor, destructive lesions on radiograph, bone scan</td>
</tr>
<tr>
<td>Multiple myeloma and lymphoma</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>or N</td>
<td>Abnormal serum or urine protein electrophoresis, abnormal bone radiographs</td>
</tr>
<tr>
<td>Humoral hypercalcemia of malignancy</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>or N</td>
<td>↑PTHrP, solid malignancy usually evident</td>
</tr>
<tr>
<td>Sarcoidosis and other granulomatous diseases</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>Hilar adenopathy, interstitial lung disease, elevated angiotensin-converting enzyme</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>↑</td>
<td>N</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>Symptoms of hyperthyroidism, elevated serum thyroxine</td>
</tr>
<tr>
<td>Vitamin D intoxication</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>Very ↑</td>
<td>N or ↑</td>
<td>History of excessive vitamin D intake</td>
</tr>
<tr>
<td>Milk-alkali syndrome</td>
<td>↑</td>
<td>N or ↓</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>History of excessive calcium and alkali ingestion, heavy use of over-the-counter calcium-containing antacids</td>
</tr>
<tr>
<td>Total body immobilization</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>or N</td>
<td>Multiple fractures, paralysis (children, adolescents, patients with Paget disease of bone)</td>
</tr>
</tbody>
</table>