

**Hypercalcemia  
Quiz  
December, 2008**

- 1) Which of the following are typical symptoms of hypercalcemia?
  - A. muscle weakness
  - B. depression
  - C. memory impairment
  - D. personality changes and psychoses
  - E. pruritus
  - F. anorexia
  - G. constipation
  - H. polyuria
  - I. cardiac arrhythmias
  - J. loss of thirst
  
- 2) What is the most common single cause of hypercalcemia?
  
- 3) Which of the following are indications for parathyroid surgery?
  - A. S.Ca > 11.0
  - B. U.Ca < 400 mg/day
  - C. Worsening DEXA
  - D. Depression and weakness
  - E. Any kidney stone
  
- 4) Which of the following are found in **Familial Hypocalciuric Hypercalcemia**?
  - A. Elevated serum calcium
  - B. Inappropriately elevated PTH
  - C. Elevated urine calcium
  - D. Hypercalcemia in half the first degree relatives
  - E. Progressive osteoporosis
  - F. Previously normal serum calcium concentration
  - G. Low serum phosphate
  
- 5) Which of the following contribute to the hypercalcemia of renal disease
  - A. Hypophosphatemia
  - B. Loss of 1-hydroxylase activity in the kidneys leading to vitamin D deficiency
  - C. Hyperplasia of the parathyroid glands
  - D. Inadequate treatment with oral calcium and rocaltrol
  - E. Over-stimulation of the parathyroid glands by Mg
  
- 6) Which of the following are appropriate tests for the initial workup of non-malignant hypercalcemia?
  - A. PTH
  - B. Phosphate
  - C. 25-OH vitamin D
  - D. 1,25 diOH vitamin D
  - E. 24 hour urine for creat, Ca, phos
  - F. DEXA
  - G. Parathyroid scan
  
- 7) What are the 3 primary mechanisms by which hypercalcemia is induced in malignancy, in order of their frequency?

- 8) Which of the following statements are true concerning malignant hypercalcemia?
- A. The hypercalcemia is usually seen early in course of the disease
  - B. Treating the hypercalcemia usually improves survival
  - C. The hypercalcemia can frequently be controlled with bisphosphonates
  - D. Tumors that commonly produce hypercalcemia are: breast, lung, head/neck, kidney, bladder, ovary, cervix, vulva, skin
  - E. The most common occult cause of malignant hypercalcemia is Multiple Myeloma
  - F. The following should be added to the usual workup for hypercalcemia if malignancy is suspected: alk phos, CBC, PTHrP, serum protein electrophoresis, 1,25 diOH VitD, appropriate x-rays, bone scan, and TNFa
- 9) Other causes of hypercalcemia are:
- A. Vitamin D intoxication
  - B. Granulomatous diseases and Sarcoidosis
  - C. Hyperthyroidism, Immobilization, Vitamin A intoxication
  - D. Pheochromocytoma, Addison crisis, Pancreatic VIPomas syndrome
  - E. Excessive oral or parenteral calcium intake
- 10) The primary cause of hypercalcemia in sarcoidosis is:
- A. High serum levels of 1,25diOH Vitamin D
  - B. Elevated PTH-related peptide
  - C. Local invasion of granulomas in bone
  - D. Sarcoid stimulation of 25-OH Vitamin D in the liver
  - E. Reduced levels of TNFa

## Answers:

1) **All except J**

2) **Primary Hyperparathyroidism (50%)** – However, it is unclear how many of these patients actually have tertiary HPTH caused by vitamin D deficiency. Certainly, if these patients are found to have hyperplasia, then tertiary HPTH needs to be considered and may impact long-term therapy.

3) **C & D:** However, everyone should be considered for surgery since this disease is frequently progressive. Clinical judgment is very important. The kidney stone should be a calcium stone.

4) **A, B, D, & G:** BEWARE! FHH is generally a benign diagnosis caused by a deactivating mutation of the calcium-sensing gene and is, therefore, not progressive. It is very bad form to operate on these people because the hypercalcemia always recurs. Only in severe cases (severe hypercalcemia >12 mg/dl, **with** symptoms) should surgery be considered. This condition cannot be cured by surgery (glands are hyperplastic not adenomatous) unless all parathyroid tissue is removed, resulting in hypoparathyroidism. Most severe cases are infants with homozygous or double heterozygous deactivating abnormalities of the calcium-sensing receptor rather than the usual heterozygous condition found in adults. The best test to distinguish from mild HPTH is the urinary calcium clearance/creatinine clearance (>0.01 likely FHH, but not always). The most definitive diagnostic findings are a previously normal serum calcium or a close relative with hypercalcemia and inappropriately elevated PTH. The only other genetic causes of HPTH are Familial Hyperparathyroidism and MEN-1 but neither presents in childhood. Activating mutations of the calcium-sensing receptor cause the opposite findings: hypocalcemia with hypercalcuria and inappropriately low serum PTH (autosomal dominant hypocalcemia (ADH)).

5) **B, C, D:** Hyperphosphatemia leads to calcium phosphate precipitation in soft tissues and hypocalcemia. 1,25 dihydroxy vitamin D cannot be synthesized without the 1-hydroxylase in the kidneys and this is the active form of vitamin D. Its primary site of action is the intestine. The preventive measures that should be taken are: phosphate binders, rocaltrol (1,25 diOH vitD), and appropriate calcium supplements. Mg is required for PTH secretion so Mg deficiency will lead to hypocalcemia with low PTH.

6) **All except D & G:** 1,25 diOH Vit D is usually only useful in patients with granulomatous disease and perhaps to assess PTH activity (it is activated by PTH) so it is usually not done initially unless there is a strong suspicion of granulomatous disease. Similarly, a parathyroid scan is not done until hyperparathyroidism is diagnosed chemically. It is not a screening test because of its high false negative rate.

7) Humoral by the production of “PTH related peptide” (~80%), local cytokine production (TNF, TGF, IL-1, prostaglandins) (~20%), and local invasion (probably < 1%).

8) **C, D, E:** F is false because a TNF $\alpha$  is not useful even if it could be ordered (it is not clinically available). The cytokines are locally produced and, therefore, the serum levels are probably not elevated. The other tests are indicated.

9) All true

10) **B:** Sarcoid granulomas produce both PTHrP and 1,25diOH-Vitamin D but it is PTHrP that appears to be the major cause of hypercalcemia since it induces bone resorption. 1,25VitD increases calcium primarily by increase Ca absorption from the gut and most of these patients ingest very little Ca. In addition, 1,25VitD directly inhibits PTHrP release and, therefore, probably helps to reduce hypercalcemia.

**Hypercalcemia**  
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**Nonspecific symptoms:** Muscle weakness, depression, memory impairment, personality changes, pruritus, anorexia, constipation, polyuria, polydipsia, shorten QT, and cardiac arrhythmias. Severe or prolonged hypercalcemia can cause corneal calcification (band keratopathy), anemia, weight loss, mental obtuseness, coma, and death.

**Causes of Hypercalcemia:**

1) Parathyroid-Related (50% of all hypercalcemia)

**Primary Hyperparathyroidism** (1:1000 pop) 80% asymp; Sx's: Nephrolithiasis and bone pain  
Adenoma (80%), Hyperplasia (15%), Multiple adenomas (<5%), Carcinoma (<5%)

Familial (sometimes - Multiple endocrine neoplasia type I or II, usually hyperplasia)

Dx: IonCa, intact PTH, Phos (x2); urine Creat, Ca, P (40% hyperCa); DEXA, x-rays?

Tx: Surgery → indications: stones and other overt signs of HPTH, progressive bone disease, symptoms, S.Ca > 12 mg/dL, U.Ca > 400 mg/day, age < 50

Most patients w/even mild disease will progress; consider surgery in all pts.

PTH will still respond to changes in IonCa.

Parathyroid scans and ultrasound can be used to localize but both have high false negative rates so a negative scan does not mean there is no disease.

Medical → Hydration, bisphosphonates, estrogen

**Familial Hypocalciuric Hypercalcemia** (autosomal dominant; benign, common condition)

Deactivating defect in calcium-sensing receptor gene in the parathyroid glands and kidneys.

Usually: PTH normal, IonCa high, U.Ca low; high Ca in half of first degree relatives!!

Dx: IonCa, intact PTH, P (x2); urine Creat, Ca, P; DEXA **Check relatives!**

Tx: none needed

**Lithium** therapy: seen in 10% of treated patients; Lithium stimulates PTH secretion

**Tertiary Hyperparathyroidism** (dialysis or renal transplant pts; vitamin D deficiency)

Chronic hypoCa leads to parathyroid hyperplasia.

Each parathyroid cell has to secrete a minimum amount of PTH → even hyperCa cannot completely suppress PTH if there are too many cells.

Dx: IonCa, intact PTH, Phos (x2); DEXA, x-rays? (urine studies not helpful)

Tx: Hydration, surgery, bisphosphonates, estrogen

2) Malignancy-associated hypercalcemia (40% of all hyperCa):

Seen in 5-10% of hospitalized patients with cancer; direct contribution to death <25%.

Aggravated by immobilization, thiazides, prerenal or renal azotemia, hypophosphatemia, or hyperalimentation.

Rarely seen with occult disease except with Multiple Myeloma

Routine imaging studies should find the cancer.

Sx: usually due to cancer; hyperCa usually seen late in course → survival <6 months

(Exception: hematologic causes)

Dx: IonCa, Phos, alk phos, CBC, iPTH, PTHrP, SPEP, 1,25OHVitD, x-rays, bone scan

Tx\*: TREAT THE CANCER; Fluids (2-4 L/day) ± lasix

Pamidronate 30-60 mg IV over 4 hrs – should respond within 7 days, repeat as needed

Zoledronic Acid 4 mg IV over 15-30 min – may repeat in 7 days

Calcitonin (25-50 U q6 hr SQ) – should respond within 24 hrs, temporary response

Treating calcium does not alter survival (myeloma?) but does improve symptoms

Local osteolytic, bone metastases (20%):

Osteoclast-activating factors (OAF's) → Cytokines produced by tumor with local effect:

TNF-alpha (cachectin), TNF-beta (lymphotoxin), TGF-alpha & beta, IL-1, Prostaglandins

**OR**

Direct bone resorption by tumor (probably minor mechanism)

Solid tumors: **breast, lung, kidney, thyroid** (breast: 50% local, 50% humoral)

Dx: normal PTHrP & Phos, (+) mets during appropriate tumor work-up

Hematologic:

**Multiple Myeloma:** bone pain in 70% (esp w/movements), cytokine mediated

Lytic lesions (usually negative bone scan), may be palpable

HyperCa symptoms may dominate course

Dx: serum immunoglobulins and immunoelectrophoresis

24-h urine: total protein and immunoelectrophoresis

Tx: as above plus glucocorticoids may be helpful

**Lymphomas:** controversial and rare if it does occur

**Leukemias:** Adult T-cell Lymphoma/Leukemia (rare) secretes both

PTHrP systemically and cytokines locally

Humoral hypercalcemia (80%): almost all "PTH-related Peptide" (PTHrP); rarely PTH or cytokines

Dx: normal PTH, low Phos, no mets with appropriate tumor work-up

**Non-small cell lung, breast, head/neck, kidney, bladder, ovary**

Esp. Squamous cell carcinomas (**head and neck, esophagus, lung, cervix, vulva, skin**)

Uncommon at presentation (<1%); 10-20% near time of death

**Lymphomas:** T cell, mixed histiocytic-lymphocytic, B cell immunoblastic → 1,25OHVitD

**Lymphoproliferative Disease**

### 3) Vitamin D-related

Dx: IonCa, PTH, PTHrP, Phos, 25OHVitD, 1,25OHVitD

Tx: Glucocorticoids may be helpful → inhibit Ca absorption, increase excretion; reduce granulomas

Vitamin D intoxication

Granulomatous diseases

Sarcoid produces both 1,25OHVitD & PTHrP; major cause of HyperCa is PTHrP;

1,25OHVitD suppresses PTHrP secretion and may, therefore, actually reduce hyperCa,

especially on low Ca diet (the major mechanism of HyperCa with 1,25OHVitD is GI hyper-absorption of Ca)

Lymphomas – as above

### 4) Increased bone turnover:

Hyperthyroidism, Immobilization, Vitamin A intoxication, Benzothiadiazide therapy

### 5) Decreased bone mineralization: Aluminum intoxication in renal failure; rare today

### 6) Endocrinopathy: Pheochromocytoma, Addison crisis, Pancreatic VIPomas syndrome

### 7) Excess PO Ca intake (rare) or Parenteral nutrition