

**Hypercalcemia**  
**Thomas A. Hughes**  
**February, 2002**

**Nonspecific symptoms:** Muscle weakness, depression, memory impairment, personality changes, pruritus, anorexia, constipation, polyuria, polydipsia, shortened 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 hyperCa)

**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, P (x2); urine Creat, Ca, P (40% hyperCa); DEXA, x-rays?

Tx: Surgery → stones, progressive bone disease, symptoms, Ca > 11.5 mg/dL

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

PTH will still respond to changes in IonCa.

Medical → Hydration, bisphosphonates, estrogen

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

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

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

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

Tx: none needed

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

**Tertiary hyperparathyroidism** (dialysis or renal transplant pts)

Chronic hypoCa has lead 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, P (x2); DEXA, x-rays? (urine not useful)

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 MM.

Routine imaging studies should find cancer.

Sx: usually due to cancer; hyperCa usually late in course, survival <6 mths

(Exception: hematologic)

Dx: IonCa, P, alk phos, CBC, iPTH, PTHrP, serum protein electrophoresis, 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 prn

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

Mithramycin 2.5-mg/kg daily – response in 3-4 days

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 →  
TNF-a (cachectin), TNF-b (lymphotoxin), TGFa,b, IL-1, PGs **or**  
Direct bone resorption by tumor (probably minor mechanism)

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

Dx: normal PTHrP & P, (+) mets (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\*, glucocorticoids may be helpful

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

**Leukemias:** Adult T-cell Lymphoma/Leukemia secretes both  
PTHrP systemically and Cytokines locally; rare

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

Dx: normal PTH, low P, no mets (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, P, 25OHVitD, 1,25OHVitD

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

Vitamin D intoxication

Granulomatous diseases, Sarcoid (excessive 1,25OHVitD production)

Lymphomas - 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 or Parenteral nutrition