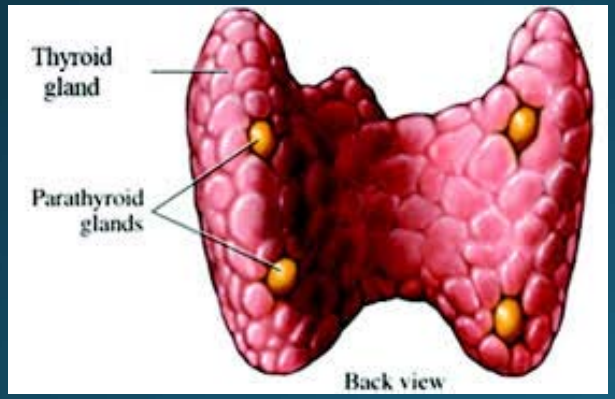

HYPERCALCEMIA

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Goal:

- Review history and physical exam in a patient presenting with hypercalcemia.
- Review laboratory investigation in a patient with hypercalcemia.
- Review various treatment options for a hypercalcemic patient

Case: 1-R.R

- 74 year old woman presented for evaluation of hypercalcemia.

TABLE 2
Clinical Manifestations of Hypercalcemia

Renal "stones"
Nephrolithiasis
Nephrogenic diabetes insipidus
Dehydration
Nephrocalcinosis

Skeleton "bones"
Bone pain
Arthritis
Osteoporosis
Osteitis fibrosa cystica in hyperparathyroidism (subperiosteal resorption, bone cysts)

Gastrointestinal "abdominal moans"
Nausea, vomiting
Anorexia, weight loss
Constipation
Abdominal pain
Pancreatitis
Peptic ulcer disease

Neuromuscular "psychic groans"
Impaired concentration and memory
Confusion, stupor, coma
Lethargy and fatigue
Muscle weakness
Corneal calcification (band keratopathy)

Cardiovascular
Hypertension
Shortened QT interval on electrocardiogram
Cardiac arrhythmias
Vascular calcification

Other
Itching
Keratitis, conjunctivitis

Case: 1- R.R

74 year old Ms. Rita was found to have hypercalcemia on routine labs. Denies personal hx of kidney stones. Has 2 grand sons with kidney stones. Denies hypercalcemia symptoms- depression, crisis with high calcium requiring hospitalization, increased thirst, urination, anorexia, nausea, vomiting, constipation, pancreatitis, peptic ulcer disease, muscle weakness, bone pain, fatigue, confusion, decreased concentration. Has excellent memory.

Case: 1-R.R

- Etiology of hypercalcemia:

Parathyroid-Dependent Hypercalcemia
Primary hyperparathyroidism
Tertiary hyperparathyroidism
Familial hypocalciuric hypercalcemia
Lithium-associated hypercalcemia
Antagonistic autoantibodies to the calcium-sensing receptor

Case: 1- R.R

- Non-PTH mediated hypercalcemia:
- PTHrP- squamous cell carcinoma of head and neck, lung, esophagus, breast, vulva,cervix, skin,renal and bladder cancer
- 1,25 dihydroxyvitamin D- lymphoma, granulomatous disease
- Adrenal insufficiency, hyperthyroidism, pheochromocytoma, islet cell tumors, acromegaly
- Renal failure, immobilization
- Medications:
- Hydrochlorothiazide
- Vitamin A excess
- Theophylline
- Milk alkali syndrome

Case 1: R.R

- Physical exam:

- Kypho scoliosis
- Spinal tenderness
- Arthritis features- genu valgus, varus, Bouchard's, Heberden's nodes
- Gait, get up and go test

Case 1: R.R- Labs

- PTH, CMP, ionized calcium, vitamin D- 25 hydroxy
- PTHrP
- 1,25 dihydroxyvitamin D
- TSH, cosyntropin stimulation test, BMP

Case 1: R. R

Nov 2015- Ionized calcium= 5.5 (slightly increased), total calcium= 10 (normal), PTH= 76 (elevated), vitamin D= 41(normal).
PTH mediated hypercalcemia.
Mild and asymptomatic.

What is the next step?

Case 1: R.R

TABLE 28-1 Indications for Surgery in Primary Hyperparathyroidism

Modified from Bilezikian JP, Khan AA, Potts JT Jr. Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Third International Workshop. *J Clin Endocrinol Metab.* 2009;94:335-339. Based on recommendations of the 2008 National Institutes of Health–sponsored "Workshop on the Management of Asymptomatic Primary Hyperparathyroidism.")

- Overt clinical manifestations of disease
  - Kidney stones or nephrocalcinosis
  - Fractures or classic radiographic findings of osteitis fibrosa
  - Classic neuromuscular disease
  - Symptomatic or life-threatening hypercalcemia
- Serum calcium >1 mg/dL above the upper limit of normal
- Creatinine clearance <60 mL/min
- Bone mineral density low (T score ≤−2.5) at any site*
- History of fragility fracture
- Young age (<50 yr)
- Uncertain prospects for adequate medical monitoring

Case 1: R.R

Nov 2015- Ionized calcium= 5.5 (slightly increased), total calcium= 10 (normal), PTH= 76 (elevated), vitamin D= 41(normal).
PTH mediated hypercalcemia.
Mild and asymptomatic.
No indication for parathyroidectomy present. DXA in Dec 2015 was normal.
Will call Ms. Rita with 24 hour urine calcium results.

Calcium, 24Hr Urine, Creatinine, 24-Hour Urine today, CMP 1 Year and Vitamin D, 25-Hydroxy to be performed in 1 Year. She is to schedule a follow-up visit 1 Year

Collection Date & Time	02/16/2016 09:16	11/25/2015 12:05
Calcium, Ionized		5.50
Fasting:		No
Calcium, Urine, Timed		
Calcium, Urine, 24 Hour	187	
Calcium, Urine, Random	13.2	
Duration (Hr):	24	
Volume (mL):	1419	

Case: 1- R.R

- The updated NIH Consensus Conference recommendations suggest that patients not treated surgically should be monitored carefully, with
  - annual measurement of serum calcium and calculation of Cl_{Cr} and
  - DXA scan Q 1-2 years

- Patients undergoing nonoperative medical management must be cautioned to
  - maintain adequate hydration,
  - avoid diuretics and
  - prolonged immobilization.

- Dietary calcium should not be restricted.

Case: 1- R.R

- Medical management of primary hyperparathyroidism:
- Used in poor surgical candidates:

- Intravenous bisphosphonates in urgent treatment
- Cinacalcet, the first calcimimetic
  - sensitizing the CASR to extracellular calcium, can reduce PTH secretion

Case 2: A.B

50 year old lady found to have hypercalcemia on routine exam

- In March 2015 , when calcium was 10.9 (high) ,ionized calcium was high and PTH was 85 (high).

Ionized calcium= 5.51 (high), PTH= 79

Collection Date & Time	03/16/2016 00:00	01/29/2016 11:22	11/30/2015 08:46	11/16/2015 11:21	09/21/2015 09:48	09/16/2015 11:28	08/20/2015 00:00
WBC, Urine	6-10						
Vitamin D, 25-Hydroxy							
Vitamin D, 25-OH, D2							< 4
Vitamin D, 25-OH, D3							47
Vitamin D, 25-OH, Total							47

Case 2: A.B, 50 years old

- Mild, asymptomatic hypercalcemia.
- PTH mediated

Results are viewed by lab short description.Patient has some multiple results on same date and time.

Collection Date & Time	03/16/2016 00:00	01/29/2016 11:22	11/30/2015 08:46	11/16/2015 11:21	09/21/2015 09:48	09/16/2015 11:28
Calcium, Ionized			5.18			5.51
Fasting:			Yes			
Calcium, Urine, Timed						
Calcium, Urine, 24 Hour					312	
Calcium, Urine, Random					9.4	
Duration (Hr):					24	
Volume (mL):					3315	

```
TECHNIQUE:
Using lunar dual energy x-ray absorptiometry, bone mineral density evaluation
was obtained.

FINDINGS:
L1-L4 AP spine:
Bone mineral density: 1.077 gm/cm2
T-score: -0.9
Z-score: -1.1

Left femoral neck:
Bone mineral density: 0.849 gm/cm2
T-score: -1.4
Z-score: -1.4

Total left hip density: 0.850 gm/cm2

Left forearm radius total:
Bone mineral density: 0.523 gm/cm2
T score: -2.5
Z score: -3.3
```

Case 2: A.B, 50 years old

Impression:

Successful localization of a large solitary well-defined parathyroid adenoma extending from the inferior pole of the right thyroid lobe with a slight retrosternal extension.

Etiology of primary hyperparathyroidism:

- Sporadic:
- Inherited:
  - MEN 1 –MEN 1 gene
  - MEN 2- MEN 2 gene
  - Hyperparathyroidism jaw tumor syndrome
    - Malignant parathyroid tumor
    - Fibrous jaw tumor
    - HRPT2 gene

Case 3:

66 year old Ms. Billie was diagnosed with Waldenstroms Macroglobulinemia, lymphoplasmacytic lymphoma, in March 2006. Was treated with plasmapheresis. Progressed to non-Hodgkin B-cell lymphoma. Her complications include motor neuropathy in hand, vocal cords and forehead. Motor neuropathy was treated with IVIG. After 2 years of treatment with low-dose chemotherapy she reached remission in December 2013. She had relapse of WM in Oct 2014.

In Jan 2015 she was hospitalized in Scottsdale Health care center with calcium= 15.7 and IgM= 3155. Was treated with IV fluids, calcitonin, diuretics and plasmapheresis. Dr. Martin Langford, her local

Sx:
Profound fatigue+, denies kidney stones, has alternating constipation and diarrhea, has significant nausea, denies vomiting, has abdominal cramps, denies falls, fractures. Has shortness of breath on less than accustomed exertion. DXA scans done in SMIL in 2004, 2010 and in 2011. Mother has osteoporosis. Currently she is on vitamin D 5000 IU BID. When she has cold she takes vitamin D 30,000 IU BID for 2 days and reports that her cold gets better.

Case 3:

Jan 8 2015:
Calcium = 15.7 , hemoglobin- 10.2, IgM= 3155, IgG= 266,beta 2 microglobulin = 12.1
Jan 22 2015 :
Calcium= 10.4 PTH= 9.

Jan 9th 2015:
Calcium= 12.3
Vitamin D= > 96
Creatinine= 1.85
PTH= 10.1
1, 25 dihydroxy vitamin D= 179 (18-72) pg/ml

Case 3:

Feb 2015:
Calcium = 13.1
Alkaline phosphatase= 80.
Creatinine= 1.14, GFR= 50.
Vitamin D= 66
1,25 dihydroxy vitamin D> 200
Ig M= 3000
S.viscosity= 2.
PTH= 9

Provider Plan	- Non PTH mediated hypercalcemia. - Hypercalcemia due to increased 1,25 dihydroxyvitamin D. - After a detailed review of results, made recommendation to start steroids. - Use prednisone for shortest duration of time at lowest possible dose to maintain normocalcemia.

Case 3:

Ms. Billie Mae was diagnosed with 1, 25 dihydroxy vitamin D mediated hypercalcemia due to lymphoma. Treatment with a chemotherapeutic agent (Ibrutinib) normalized calcium level. She continues to be on Ibrutinib 420 mg 3 tabs once a day. Today she is feeling great with no complaints. Developed a skin rash due to ibrutinib, but resolved. Has alternating constipation and diarrhea due to Ibrutinib. Does not have other side effects which are palpitations, pneumonia.

April 20th 2015:
Vitamin D= 94.7 (30-100)
LDH= 169 (119-226)
PTH= 26 (15-65)
Calcium is 9.6 (8.7-10.3)

Provider Plan	- Non PTH mediated hypercalcemia. - Hypercalcemia due to increased 1,25 dihydroxyvitamin D, due to lymphoma. - After treatment with ibrutinib for lymphoma, calcium level normalized. Lymphoma is under better control. Ig M level decreased from 3000 to 700.

Treatment of severe hypercalcemia:

Therapy	Usual Dose	Frequency
Rehydration	2-4 L/day of 0.9% NaCl IV	qd × 1-5 days
Furosemide	20-40 mg IV (after rehydration)	q12-24hr
Pamidronate	60-90 mg IV over 2-4 hr	Once
Zoledronate	4 mg IV over 15-30 min	Once
Calcitonin	4-8 IU/kg SC	q12-24hr
Gallium nitrate	200 mg/m^2 IV over 24 hr	qd × 5 days
Glucocorticoids	200-300 mg hydrocortisone IV	qd × 3-5 days
	40-60 mg prednisone PO	qd × 3-5 days
Dialysis		

Treatment of severe hypercalcemia:

- The aggressiveness with which the individual patient is rehydrated must be considered in relation to both the
- patient's volume status and the
  - risk of precipitating or aggravating congestive heart failure or ascites
  - Diuretics, particularly thiazides, should be discontinued.
  - The use of furosemide to promote calciuresis may exacerbate extracellular volume depletion. Should be avoided.

Treatment of severe hypercalcemia:

- Bisphosphonates:
- Intravenous bisphosphonates rapidly inhibit bone resorption.

- Bisphosphonates should not be used in patients with milk-alkali syndrome, in whom they are likely to induce post-treatment hypocalcemia.

- Serum calcium usually declines within 24 hours and reaches a nadir within 1 week after a single infusion, at which point calcium levels may be normal in 70% to 90% of treated patients

Treatment of severe hypercalcemia:

- Calcitonin:
- Directly inhibits osteoclast function

- Calcitonin rarely produces a decline in serum calcium of more than 1 to 2 mg/dL.

- Efficacy typically is limited to a few days at most, possibly because of receptor downregulation in target cells of bone and kidney.

- Transient nausea, vomiting, abdominal cramps, flushing.