

HYPERCALCEMIA
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BUMC-P_

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 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.

Clinical scenario-3-

- 68 yr old lady with no PMHx was admitted for evaluation of hypercalcemia.
- 1 month ago, she noticed weakness, numbness in both legs. In addition, she had anorexia, 10 lb weight loss, fatigue. Pt was evaluated by PCP and diagnosed with depression. Pt was treated with sertraline.
- Eventually, she was taken to a hospital in Casa Grande for evaluation of encephalopathy and was found to have calcium= 15.8 mg/dl. She was treated with fluids, calcitonin, alendronate and transferred to BUMC-P.
- A month prior to the onset of her symptoms, she had a several day episode of nonbloody diarrhea and cough. These symptoms had resolved at the time of presentation. She presented with two week history of constipation.

Clinical scenario-3

	April 11 2016
Total calcium (8.3-10.4 mg/dl)	15
Ionized calcium (4.52-5.28 mg/dl)	>8
S. Phosphorus (2.5-4.5 mg/dl)	1
S. PTH (15-65 pg/ml)	<6
PTH related peptide (14-27 pg/ml)	96
25 hydroxy vitamin D (30-100 ng/ml)	10.7
Total 1,25 dihydroxy vitamin D (18-72) pg/ml	41
Calcium, normalized to creatinine (10-320 mg/gm)	1067
GFR in ml/min/m ²	47
Albumin (3.3-4.9 g/dl)	2.9
Alkaline phosphatase (41-151 IU/L)	22

Severe ,symptomatic non –PTH mediated hypercalcemia

Clinical scenario-3

- She was treated with IV fluids and calcium level was periodically monitored.
 - Since there was concern for malignancy, CT chest , abdomen, pelvis was done. Large primary rectal cancer with extensive associated lymphadenopathy extending up the retroperitoneum was seen.
 - Biopsy of rectal mass showed large cell neuroendocrine carcinoma.
 - Since she had stage IV neuroendocrine tumor she was initiated on palliative chemotherapy with cisplatin and etoposide.
 - Since then, she has progression of disease, unresponsive to chemotherapy and persistent malignant hypercalcemia. She has been placed in hospice care and most recent admission was in Aug 2016 for management of diarrhea.
-
- **Large cell neuroendocrine tumor of rectum with malignant hypercalcemia**

Clinical scenario-3

LABORATORY	08/11/2016 04:15 MST	08/10/2016 17:10 MST	08/10/2016 03:00 MST	08/09/2016 19:52 MST	08/09/2016 04:08 MST	08/09/2016 04:00 MST
<input type="checkbox"/> BUN, POC						
<input type="checkbox"/> Creatinine	1.05 *	0.98 *	1.12 *		1.16 *	
<input type="checkbox"/> Creatinine, POC						
<input type="checkbox"/> Estimated Glomerular Filtration Rate	55 * L	60 *	51 * L		49 * L	
<input type="checkbox"/> BUN/Creat Ratio	14	13	12		11	
<input type="checkbox"/> Sodium	139	140	141		138	
<input type="checkbox"/> Sodium, POC						
<input type="checkbox"/> Potassium	4.3	3.6	3.3 L		3.9	
<input type="checkbox"/> Potassium, POC						
<input type="checkbox"/> Chloride	107	108	106		104	
<input type="checkbox"/> Chloride, POC						
<input type="checkbox"/> CO2	20 L	21	23		25	
<input type="checkbox"/> Anion Gap	12	11	12		9	
<input type="checkbox"/> Magnesium	2.0		2.0		2.6 H	
<input type="checkbox"/> Calcium	12.8 H	11.5 H	12.8 H		14.9 ' C	
<input type="checkbox"/> Ionized Calcium	7.42 ' C		7.90 ' C			>8.00 ' C
<input type="checkbox"/> Ionized Calcium, POC						
<input type="checkbox"/> Phosphorus	1.5 L	1.6 L	1.8 L			

Clinical Scenario-4

- 65 year old lady was found to have calcium level of 15 mg/dl in routine evaluation and referred to an endocrinologist for evaluation.
- She was recently diagnosed with stage 1 invasive ductal breast cancer.
- Symptoms of hypercalcemia- GERD, osteoporosis. Pt denied other symptoms of hypercalcemia.
- No family history of hypercalcemia, hyperparathyroidism was present. Patient was taking hydrochlorothiazide.

Clinical Scenario-4

- PMHx: Anxiety, HTN, obesity
- PSHx: Cholecystectomy, TAH with BSO, resection of colon polyp.
- Social Hx: Single, no hx of tobacco, recreational drug use. Drinks wine 5 times / week. Has 1 child.

Clinical Scenario-4

- Physical exam:
- General: Obese lady
- Neck: No goiter, no clinically palpable nodules, neck masses
- CVS: Rhythm is normal, no murmurs, rubs
- RS: No wheezing. Chest clear to auscultation
- Musculoskeletal: No kyphoscoliosis
- Abd: Soft, non tender, no organomegaly

	March 2014	June 2016	July 2016
Total calcium (8.3-10.4 mg/dl)	11.2	12.4	14.3
Ionized calcium (4.52-5.28 mg/dl)		6.8	
Intact PTH (15-65 pg/ml)		308	525
PTH related peptide (14-27 pg/ml)			7
25-OH Vitamin D (30-100 ng/ml)			30
1,25 dihydroxyvitamin D (18-72 pg/ml)			< 8
Creatinine, Serum (0.6-1.5 mg/dl)			1.8
GFR (>60 ml/min/m ²)			43
24 hr Urine Calcium (100-300 mg/day)			1087
24 hr Urine Creatinine (0.63-2.5 g/day)			1.65

Clinical scenario-4

- DXA done in 2015

Lumbar 0.84 gm/cm² T-score -2.9

Femoral 0.755 gm/cm² T-score -2.0

ASSESSMENT:

The BMD measured at AP Spine L1-L4 is 0.840 g/cm² with a T-score of -2.9. This patient is considered osteoporotic according to World Health Organization (WHO) criteria. Fracture risk is high. Pharmacological treatment, if not already prescribed, should be started. A follow up bone density test is recommended in one year to monitor response to therapy.

Site	Region	Measured Date	Measured Age	WHO Classification	Young Adult T-score	BMD
AP Spine	L1-L4	05/29/2015	64.1	Osteoporosis	-2.9	0.840 g/cm ²
Dual Femur	Neck Left	05/29/2015	64.1	Osteopenia	-2.0	0.755 g/cm ²
Dual Femur	Neck Right	05/29/2015	64.1	Osteopenia	-2.4	0.706 g/cm ²
Dual Femur	Total Left	05/29/2015	64.1	Osteopenia	-1.2	0.854 g/cm ²
Dual Femur	Total Right	05/29/2015	64.1	Osteopenia	-1.8	0.786 g/cm ²

World Health Organization (WHO) criteria for post-menopausal, Caucasian Women:

Normal: T-score at or above -1 SD

Osteopenia: T-score between -1 and -2.5 SD

Osteoporosis: T-score at or below -2.5 SD

Clinical scenario-4

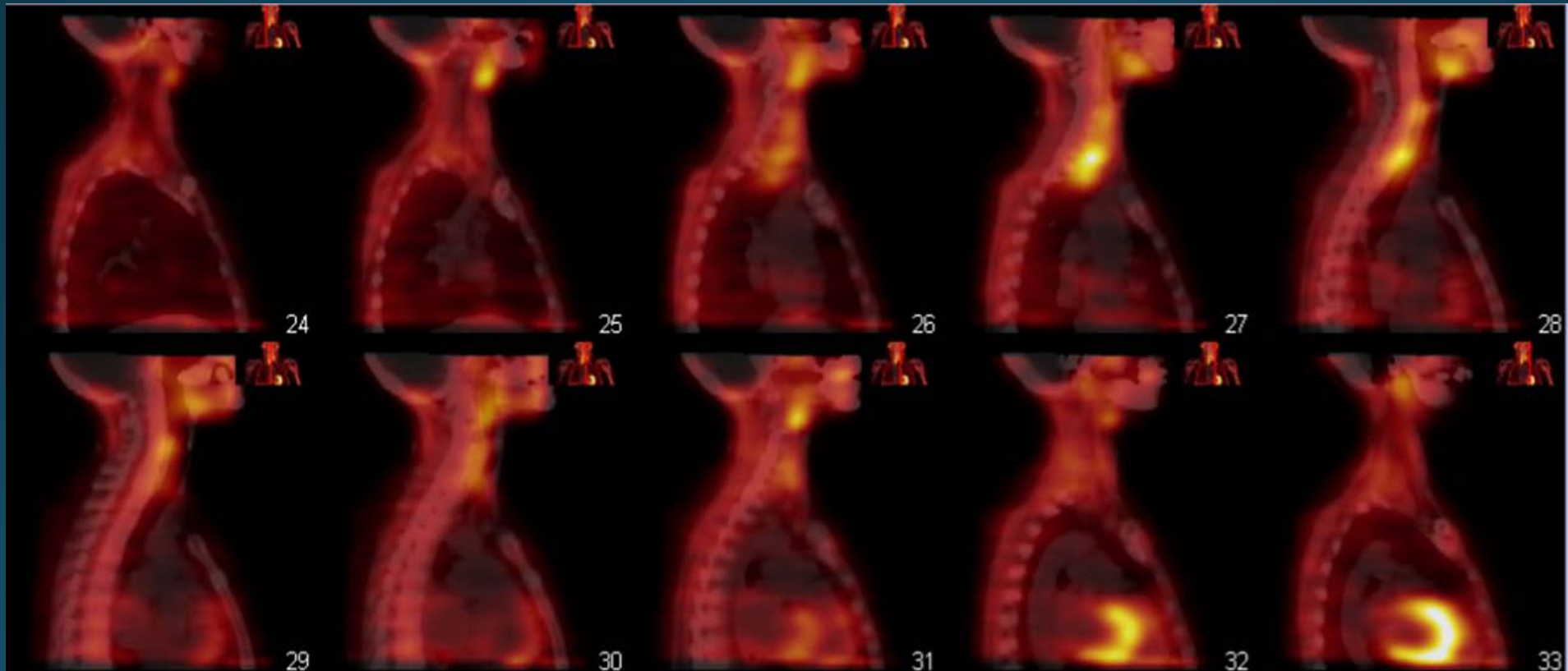
- What is the diagnosis?

Severe, symptomatic PTH-mediated hypercalcemia

- What is the next step in management?

Clinical scenario-4

- Sestamibi scan



Clinical scenario-4



Abnormal parathyroid imaging study with SPECT with scintigraphic evidence of a prominent focus of increased tracer labeling in relation to the inferior , posterior aspect of the right lobe of thyroid consistent with an parathyroid adenoma.

Clinical scenario-4

- In July 2016, patient underwent focused parathyroidectomy with excision of right inferior parathyroid adenoma that was located in retrosophageal area.

Date	Baseline PTH (12-88 pg/ml)	PTH in 10 minutes	Calcium (8.4-10.6 mg/dl)
07-15-16	706	234	
07-16-16	18		10

Clinical scenario-4



14,700 mg adenoma
(Normal parathyroid weight is 30 mg)

Diagnosis:

Right upper parathyroid, resection:

- Parathyroid adenoma (14.7 grams).

LOUIS JNOVOA-TAKARA MD Verified:07/19/16

(Electronic Signature)

LJN/ARC

Location: Banner -- University Medical Center Phoenix, 1111 E. McDowell Road, Phoenix AZ. 85006

HYPOCALCEMIA

Clinical scenario-1

- 28 year old L.M with history of mental retardation was diagnosed with non toxic multinodular goiter.
- Patient was anxious about periodic FNA to monitor thyroid nodule.
- Patient's mother decided to proceed with total thyroidectomy.
- Total thyroidectomy was performed in Nov 2014.
- POD 1 total calcium was 7.7 mg/dl and patient was discharged on calcitriol 0.25 mcg QD.

Clinical scenario-1

Nov 24 2014	
Total calcium (8.7-10.4 mg/dl)	7.8 mg/dl
Phosphorus (2.5-4.5 mg/dl)	5
PTH (15-65 pg/ml)	7
Vitamin D (30-100 ng/ml)	30.2

Hypocalcemia with low PTH- Hypoparathyroidism

How to differentiate hypoparathyroidism from hungry bone syndrome?

Clinical scenario-1

- Mild, asymptomatic hypocalcemia
- Treat with calcitriol and calcium carbonate to increase calcium to low end of normal range
- If calcium is maintained in normal range , hypercalciuria may occur

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

Collection Date & Time	05/16/2016 10:29	01/08/2016 09:30	09/02/2015 08:45	05/29/2015 15:46	02/20/2015 15:06	12/16/2014 10:33	11/24/2014 14:15
Hemoglobin A1c	<u>5.5</u>		Cancelled				
Intact PTH							
Intact PTH				<u>21</u>	<u>10</u>	<u>10</u>	<u>7</u>
Phosphorus (Inorganic)							
Phosphorus (Inorganic)						3.6	5.0
PTH Intact and Calcium							
Calcium		9.1					
Intact PTH		<u>22</u>					