THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

A 47-year-old man with hypercalcemia

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Adult and Pediatric Endocrinology Fellow
1/30/2024

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Dr. Winer does not have any relevant financial relationships with any commercial interests.

Objectives

- Discuss the differential of hypercalcemia
- Discuss treatment options for hypercalcemia

HPI

- 47-year-old man with rheumatoid arthritis presents to the ED for bilateral knee pain
- Chronic bilateral knee pain with multiple trips to the ED.
- Has not established with a PCP or rheumatologist
- Pain is unresponsive to OTC medications
- This episode is associated with new right calf swelling and pain

- ROS: denies fevers, chills, diaphoresis, wt loss, CP, SOB, palpitations, cough, N/V/D, constipation, changes in BM, urinary symptoms, dizziness, headaches or any additional complaints.

History

Medical:

- RA (?)
- Anemia
  - Received blood transfusions during ED visits without further evaluation

Surgical:

- Denies

Family:

- Mom with RA
- No known calcium disorders, kidney stones

Social:

- Lives with Mother and son
- Previously incarcerated
  - Acquired tattoos while admitted
- Multiple unprotected sexual partners

Medications:

- OTC NSAIDs and acetaminophen

Physical Exam

BP 95/59 | Pulse 120 | T 37.4 ℃ | RR 17 |
Wt 54.6 kg (120 lb) | Ht 6'0" | BMI 16.28

General: In no acute distress, thin
HEENT: **dry mucous membranes, pale conjunctivae**
Neck: no thyromegaly
Cardiovascular: **Tachycardia,** regular rhythm, **delayed cap refill**
Pulmonary: clear to auscultation bilaterally
Abdominal: Abdomen is soft and flat
Musculoskeletal: Limited ROM of knees b/l to flexion and extension, **RLE 2+ edema,** no LLE edema
Skin: no obvious rashes
Neurological: A&Ox3, no focal deficits

Evaluation

Glu 137
Na 129
K 4.2
Cl 96
CO2 18
BUN 11
Cr 0.76
BHOB 0.11

Ca 11.9
Mg 1.6
Phos 2.0
Alb 2.1
Total Protein 7.9
Alk Phos 166
AST 18
ALT 9
Cortisol: 24.7 (9am)

WBC 12.4
Hg 3.4
Hct 14.3
MCV 68.1
Plt 458

TSH: 0.91
Total T4: 4.1
A1c: 5.3%

Lab interpretation and next steps?

Corrected Ca: 13.4

Admission

#Failure to thrive/weight loss
#Microcytic Anemia:
#RLE swelling
#Acute on chronic B/L Knee Pain
#Rheumatoid arthritis
#Hypercalcemia
#Hypovolemic Hypochloremic Hyponatremia
#HAGMA

Ordered extensive work up including:

- STI screening
- Venous dopplers
- Pan CT scans

Further evaluation

HIV + with CD4 count of 66
Syphilis +
Quant Tb Gold indeterminate

Doppler: Multiple DVTs

CT Chest/Abdomen/Pelvis:
- Calcified hilar granulomas bilaterally
- Fungating mass in the medial thighs, possibly condyloma acuminatum

Further evaluation

- Patient allowed physical exam
- GI and Colorectal surgery consulted
- Procedures delayed until Tb (airborne) precautions could be discontinued

Returning to Patient's Calcium levels

	Latest Reference Range & Units	10/22/24 21:52	10/24/24 04:13
Calcium	8.4 - 10.2 mg/dL	**11.9 (H)**	**11.2 (H)**
Inorganic Phosphate	2.5 - 4.4 mg/dL		
Magnesium	1.6 - 2.5 mg/dL		
Albumin	3.5 - 5.0 g/dL	**2.1 (L)**	
Corrected Ca		**13.4**	
PTH, Intact	15 - 75 pg/mL	**<6 (L)**	
25-Hydroxy Vitamin D	20 - 99 ng/mL		

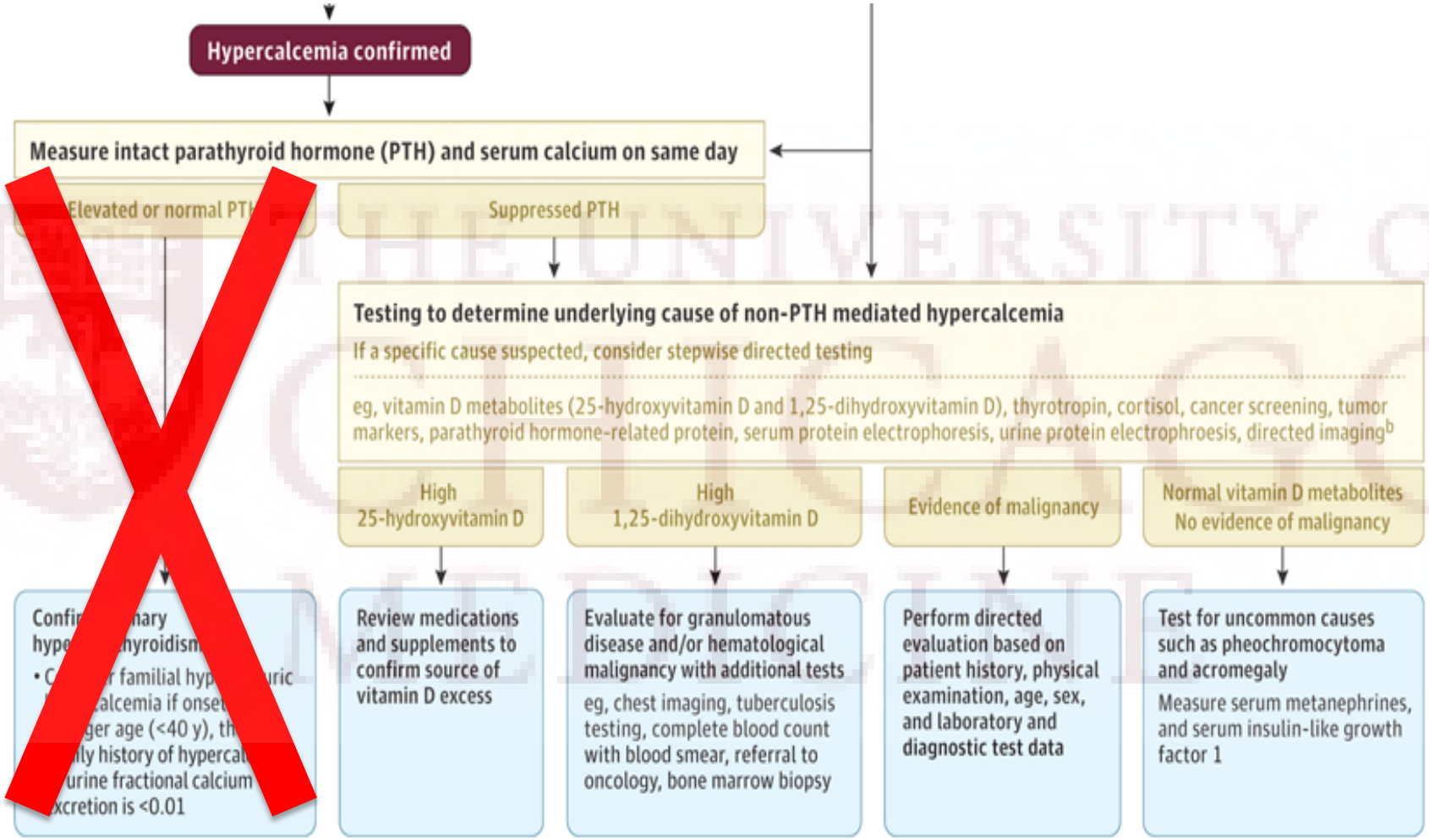
On hyperhydration

Pending:
PTHrP
25 Vit D
1,25 (OH)2 Vit D

We have PTH-independent hypercalcemia

What is highest on your differential?

Differential of PTH-Independent Hypercalcemia



(Walker, M and Shane, E, 2022)

HIV/AIDS-associated Hypercalcemia

1,25-mediated
- Tuberculosis
- Histoplasmosis
- PJP pneumonia
- Cat-Scratch fever
- Immune reconstitution inflammatory syndrome

Likely 1,25-mediated
- Mycobacterium avium complex
- Candidiasis
- Coccidioidomycosis
- Paracoccidioides
- Leishmaniasis
- Foreign material reactions

PTHrP-related
- HIV-associated Lymphadenopathy
- **Coccidioidomycosis**

Mechanism not fully elucidated
- Leprosy
- CMV
- Cryptococcus neoformans
- Adrenal insufficiency

Lymphoproliferative disorders

Not all PTHrP-related hypercalcemia is due to malignancy!

Hypercalcemia in Disseminated Coccidioidomycosis: Expression of Parathyroid Hormone–Related Peptide Is Characteristic of Granulomatous Inflammation

Joshua Fierer ✉, Douglas W. Burton, Parviz Haghighi, Leonard J. Deftos

Clinical Infectious Diseases, Volume 55, Issue 7, 1 October 2012, Pages e61–e66,

Returning to patient's calcium levels

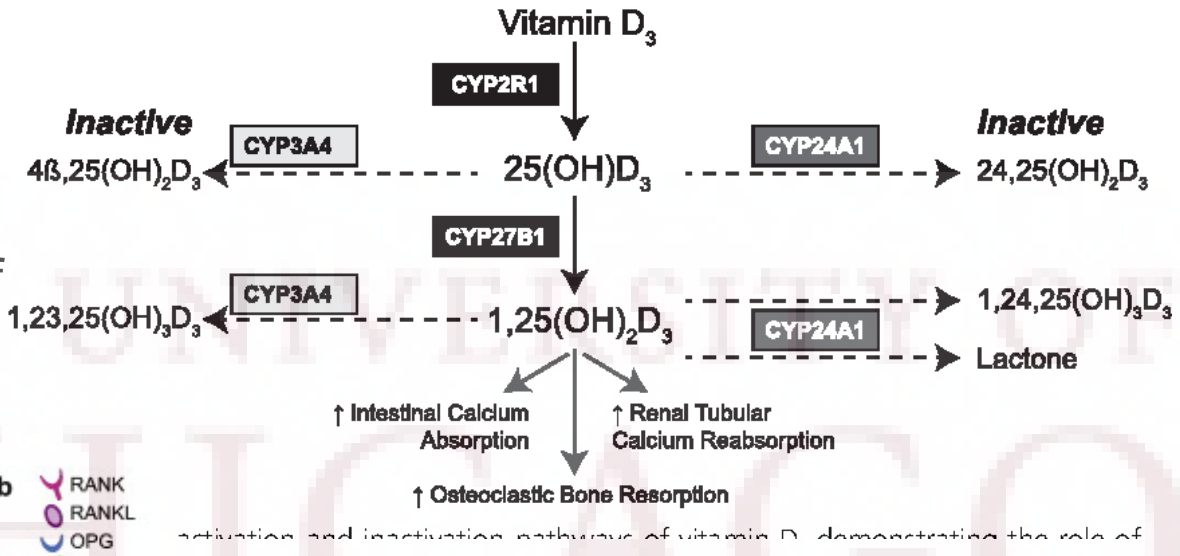
	Latest Reference Range & Units	10/22/24 21:52	10/24/24 04:13	10/25/24 06:21	10/26/24 05:20
Calcium	8.4 - 10.2 mg/dL	**11.9 (H)**	**11.2 (H)**	**11.2 (H)**	**12.4 (H)**
Inorganic Phosphate	2.5 - 4.4 mg/dL			**2.0 (L)**	**2.1 (L)**
Magnesium	1.6 - 2.5 mg/dL			1.6	1.7
Albumin	3.5 - 5.0 g/dL	**2.1 (L)**		**2.0 (L)**	**1.8 (L)**
Corrected Ca		**13.4**		**12.8**	**14.2**
PTH, Intact	15 - 75 pg/mL	**<6 (L)**			
25-Hydroxy Vitamin D	20 - 99 ng/mL			**<6 (L)**	

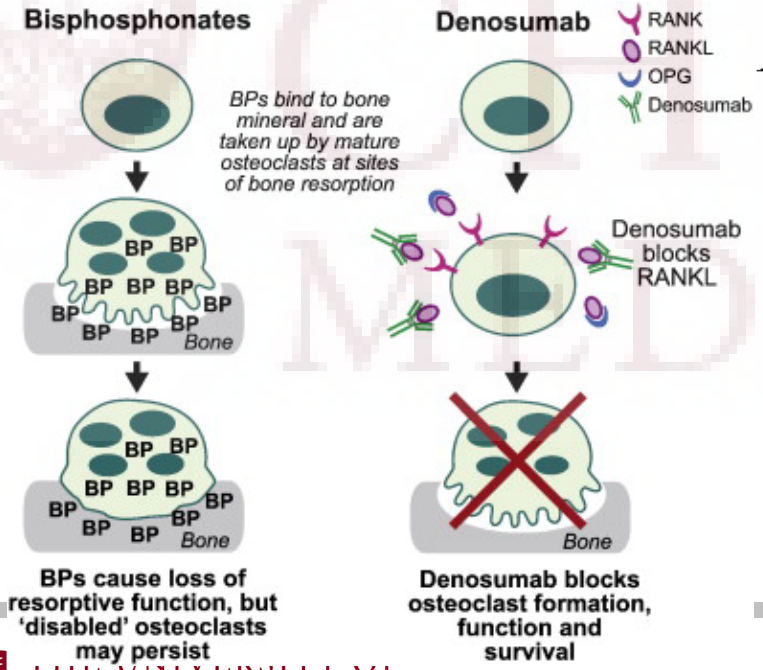
Would you change treatment course?

Treatment of PTH-independent hypercalcemia

Steroids:

- Inhibition of 1-alpha-hydroxylase
- Increased expression of 24-hydroxylase





Bisphosphonates:

- Inhibit osteoclast action by binding calcium hydroxyapatite

Denosumab:

- Binds RANKL

Returning to Patient's Calcium levels

	Latest Reference Range & Units	10/22/24 21:52	10/24/24 04:13	10/25/24 06:21	10/26/24 05:20
Calcium	8.4 - 10.2 mg/dL	11.9 (H)	11.2 (H)	11.2 (H)	12.4 (H)
Inorganic Phosphate					
Magnesium					
Albumin	3.5 - 5.0 g/dL	2.1 (L)		2.0 (L)	1.8 (L)
Corrected Ca		13.4		12.8	14.2
PTH, Intact	15 - 75 pg/mL	<6 (L)			
25-Hydroxy Vitamin D	20 - 99 ng/mL			<6 (L)	

Patient NOW trying to leave AMA!
What should we pivot too?

Treatment course

- Counseled on risks of AMA
- Gave Zoledronic Acid 4mg IV
- Started calcitonin 4 units/kg q12 hours for as many doses as possible
- Gave Vit D3 50,000 IU once

PTHrP: 7.1
(<4.2pmol/L)
1,25-OH Vit D: 16
(18 -64 pg/mL)

	10/26/24	10/27/24	10/28/24	10/29/24	10/30/24
Calcium 8.4 - 10.2 mg/dL	**12.4 (H)**	**12.0 (H)**	**10.4 (H)**	**10.6 (H)**	10.0
Albumin 3.5 - 5.0 g/dL	**1.8 (L)**	**1.9 (L)**	**2.2 (L)**	**2.2 (L)**	**2.2 (L)**
Corrected Ca					

Patient left AMA on 10/30/24. Discharged on Vit D3 2000 IU daily

Representation

- Presented two weeks later due to AMS
- Admission labs:

	11/14/24 16:12	11/14/24 22:51	11/15/24 06:26
Calcium 8.4 - 10.2 mg/dL	**13.3 (HH)**	**12.4 (H)**	**12.0 (H)**
Albumin 3.5 - 5.0 g/dL		**1.9 (L)**	

- Primary team gave ZA on 11/14
- Endocrine consulted 11/15
  - calcitonin 4 units/kg q12 hours x 48 hours
  - start Vitamin D3 1000 units daily

Further calcium levels

	11/14/24	11/15/24	11/16/24	11/17/24	11/18/24	11/19/24	11/19/24	11/20/24
Calcium 8.4 - 10.2	**12.4 (H)**	**12.0 (H)**	**11.8 (H)**	**12.0 (H)**	**12.0 (H)**	**11.5 (H)**	**12.1 (H)**	**11.3 (H)**
Albumin 3.5 - 5.0	**1.9 (L)**		**2.3 (L)**	**2.1 (L)**	**2.3 (L)**	**2.1 (L)**		**1.9 (L)**

Next steps?

Patient given denosumab 120mg IV

ZA-Refractory Hypercalcemia of Malignancy: Risk Factors

TABLE I—CONCENTRATION (pmol/L) PTHrP AND PRIMARY TUMOUR

Diagnosis	PTHrP (no of patients)			
	<2·0	2·0–10·0	10·0–20·0	>20·0
Breast	3	7	3	5
Lung carcinoma				
Adenocarcinoma	1			
Large cell			1	1
Squamous cell		1	1	2
Small cell	1			
Renal		2	2	
Prostate	2		1	
Ovary, clear cell		1		1
SCC, palate			1	
TCC bladder			1	1
Colon		1		1
Malignant melanoma	1			
ACUP		1		
Phaeochromocytoma	1			
NHL		1		

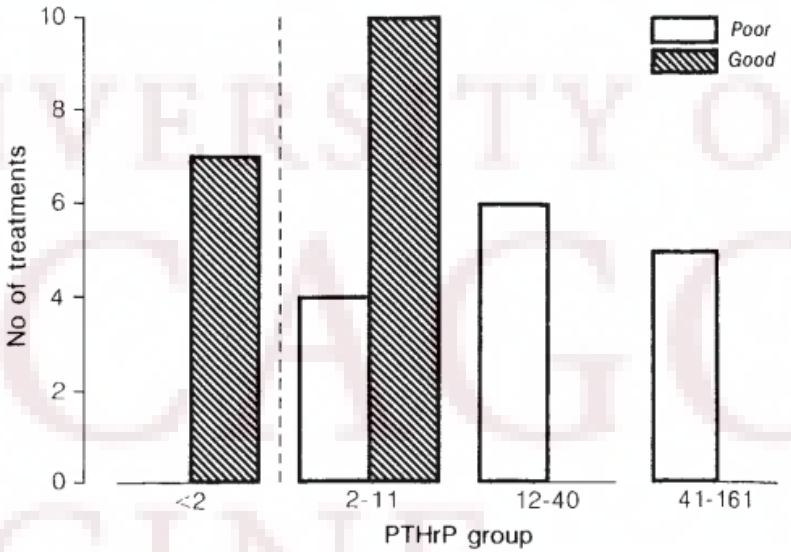


Fig 2—PTHrP levels according to response category (pmol/L).
- - - indicates assay detection limit.

Our patient's PTHrP values: 7.1, 22

ZA-Refractory Hypercalcemia of Malignancy: Risk Factors

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	Time to relapse median (days)	Relative risk
Tumor type		
Hemopoietic system	>28	1.00
Breast	26	1.36
Kidney, urinary, and digestive tracts, and unspecified	15	2.23
Lung and upper respiratory tract	11	3.43
Sex		
Male	15	1.00
Female	25	0.55
Age		
<50 yr	26	1.00
>50 yr	16	1.52

ZA-Refractory Hypercalcemia of Malignancy: Risk Factors

Response to ZA associated with:

- Degree of PTHrP elevation
- Co-elevation of 1,25-OH

	Norma range	Lung and upper respiratory tract	Breast	Hemopoieti system	Kidney, urinary, and digestive tracts and unspecified
No. of patients		61	76	34	129
Albumin (g/L)	35–45	28.9 ± 0.6	32.9 ± 0.6	31.1 ± 1.2	30.8 ± 0.6
Albumin-corrected calcium (mmol/L)	2.2–2.7	3.26 ± 0.04	3.43 ± 0.05	3.42 ± 0.06	3.35 ± 0.04
Inorganic phosphate (mmol/L)	0.8–1.4	0.88 ± 0.03	1.06 ± 0.04	1.40 ± 0.12	0.90 ± 0.03
Creatinine (mmol/L)	0.05–0.12	0.10 ± 0.00	0.12 ± 0.01	0.19 ± 0.02	0.11 ± 0.01
PTHrP (pmol/L)	<2.5	5.7 ± 0.6	4.0 ± 1.0	1.5 ± 0.3	5.9 ± 0.9

ZA-Refractory Hypercalcemia of Malignancy

Denosumab for Treatment of Hypercalcemia of Malignancy

Mimi I. Hu ✉, Ilya G. Glezerman, Sophie Leb
Waldemar Misiorowski, Bennett Yu, Paul Zo
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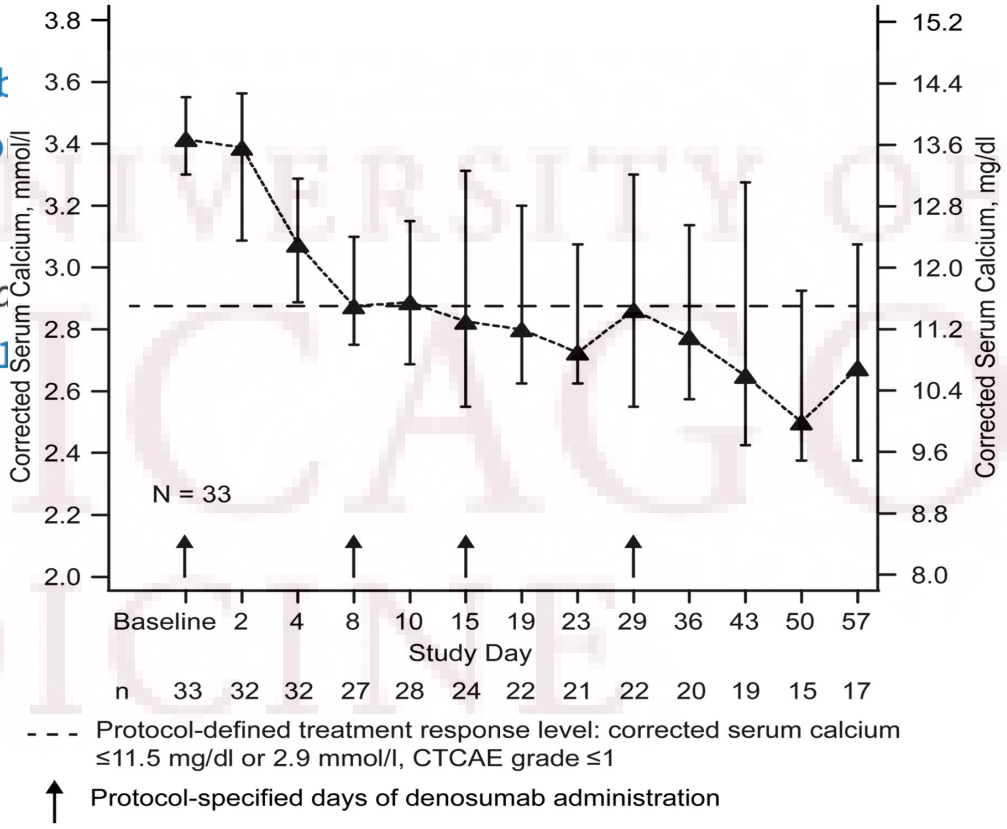
The Journal of Clinical Endocrinology & Meta
2014, Pages 3144–3152, https://doi.org/10.1

- Open label Phase 2 study
- ~35 patients with ZA refractory hypercalcemia
  - Ca >12.5
  - Average of 4 doses of ZA
  - At least 7 days since last dose
- Given Denosumab 120mg on on days 1, 8, 15, and 29 and every 4 weeks thereafter



Returning to our patient

	11/20	11/21	11/22	11/23	11/23	11/24	11/25	11/26	11/26
Calcium8.4 - 10.2 mg/dL	**10.8 (H)**	8.4	**8.1 (L)**	**7.8 (L)**	**7.8 (L)**	**7.3 (L)**	**6.9 (L)**	**6.9 (L)**	**6.9 (L)**
Albumin3.5 - 5.0 g/dL		**1.8 (L)**	**1.8 (L)**	**1.9 (L)**	**1.9 (L)**	**1.8 (L)**	**1.6 (L)**	**1.7 (L)**	

- Mild hypocalcemia; did not start treatment
- Admission AMS improved; thought to be multifactorial (including hypercalcemia)
- Discharged to SAR
- FU with Endocrine, ID and biopsy of mass scheduled

Returning to our patient

- Presented to ID clinic in early Jan
- Found to be in septic shock
  - Fulminant c. diff infection
  - Necrotizing ulcerative perineal mass
  - Acute toxic metabolic encephalopathy
- Ongoing GOC discussions
- Developed Hypercalcemia on hospital day 21, endocrinology not yet consulted

Take Home Points

- PTH-independent hypercalcemia can be due infectious etiologies through a granulomatous pathway

- Risk factors for refractory zoledronic acid include higher PTHrP levels

- Denosumab is effective in ZA-refractory hypercalcemia

Thanks to Dr. Jain and Dr. Sam!

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