THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"A 54y male with hypercalcemia"

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

Objectives

- Discuss the diagnosis and presentation of hypercalcemia in sarcoidosis
- Discuss the role of Vitamin D in sarcoidosis
- Discuss the management strategies for steroid resistant hypercalcemia in sarcoidosis

UCMC Presentation

- 54yM presents to the ED after being told by his outpatient pulmonologist that his lab work was concerning
- Reports that he was in his usual state of health, with no symptomatic complaints

Temperature	97.7°F
Heart Rate	102 bpm
Blood Pressure	132/87
Respiratory Rate	16
SpO2	97% on room air

Medical History

- No surgical history
- No known family history of kidney disease, autoimmune conditions, or malignancy
- Former smoker (1-2ppd) quit in 2022
- Previously drank 12 beers daily, had a prolonged period of sobriety but has started drinking alcohol again

Gen: No fatigue, fevers, or chills, appropriate appetite **lost 40lbs unintentionally** but has since gained weight back

Eyes: No change in vision, eye pain, or discharge;

ENT: No congestion, or sore throat.

CV: No CP, edema

Resp: No SOB, cough

GI: No abdominal pain, nausea, vomiting, diarrhea, constipation

GU: No dysuria, hematuria

MS: No weakness, joint swelling, joint pain

Skin: No rashes, Raynaud's

Neuro: No numbness/tingling, headaches, confusion or decreased concentration

Heme: + palpable cervical lymphadenopathy

Outpatient labs

	Latest Reference Range & Units	
Sodium	135 - 145 mmol/L	132 (L)
Potassium	3.5 - 5.0 mmol/L	4.5
Chloride	98 - 108 mmol/L	97 (L)
Carbon Dioxide	23 - 30 mmol/L	26
Anion Gap	6 - 15 mmol/L	9
BUN	7 - 20 mg/dL	28 (H)
Creatinine	0.50 - 1.40 mg/dL	2.63 (H)
eGFR, All	>=90 mL/min/1.73 sq. m	28 (L)
Calcium	8.4 - 10.2 mg/dL	15.4 (HH)
Total Protein	6.0 - 8.3 g/dL	7.5
Albumin	3.5 - 5.0 g/dL	4.0
Bilirubin, Total	0.1 - 1.0 mg/dL	0.4
Bilirubin, Conjugated	0.0 - 0.3 mg/dL	0.2
Bilirubin, Unconjugated	0.1 - 1.0 mg/dL	0.3
Alk Phos, Serum	30 - 120 U/L	229 (H)
AST (SGOT)	8 - 37 U/L	23
ALT (SGPT)	8 - 35 U/L	13

Notable findings?

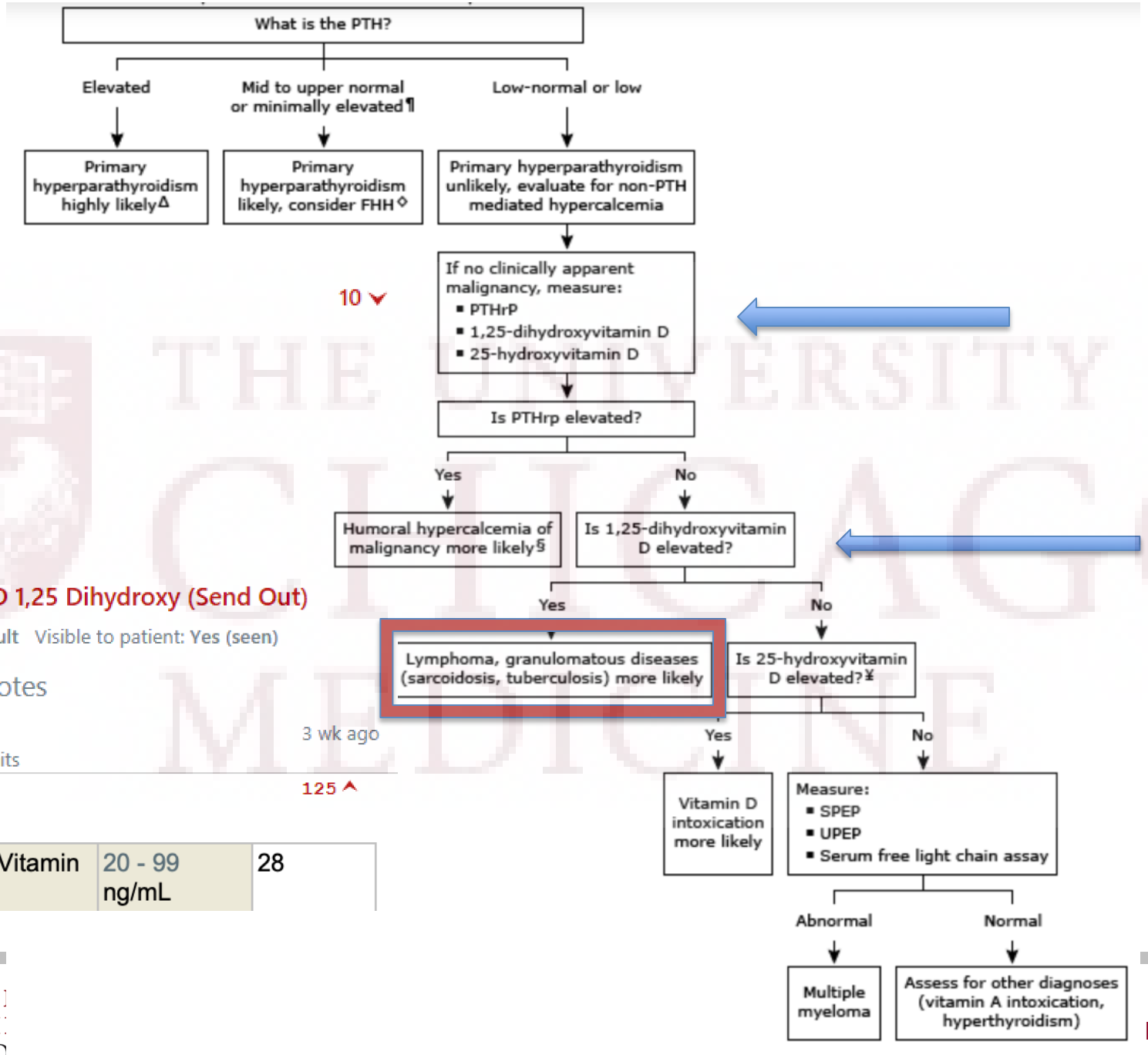
Next labs?

OSH presentation

- Patient reports that he had a similar admission at an outside hospital ~6 months earlier

SODIUM	140
POTASSIUM	4.6
CHLORIDE	103
CO2	30
ANION GAP	7
BUN	27 ↑
CREATININE	2.56 ↑
GLUCOSE	92
ALBUMIN	3.9
PROTEIN, TOTAL	6.9
CALCIUM	14.9 ↑↑
ALKALINE PHOSPHATASE	150 ↑

INTACT PTH	<4 ↓
CALCIUM, FOR PTH	13.1 ↑↑



PTH-RP 10

Vitamin D 1,25 Dihydroxy (Send Out)

Status: Final result Visible to patient: Yes (seen)

0 Result Notes

Component Ref Range & Units	3 wk ago
Vitamin D 18 - 64 pg/mL	125 ^

25-Hydroxy Vitamin D	20 - 99 ng/mL	28

OSH admission

Impression

1. EXTENSIVE MEDIASTINAL AND BILATERAL HILAR ADENOPATHY CONSISTENT WITH MALIGNANCY. THIS RAISES POSSIBILITY OF METASTATIC DISEASE OR LYMPHOMA. CLINICAL CORRELATION IS ADVISED.

2. EXAMINATION NEGATIVE FOR FOCAL CONSOLIDATION.

3. A FEW SCATTERED 5 MM OR LESS NONCALCIFIED NODULAR DENSITIES ARE NOTED IN THE LUNGS BILATERALLY THAT ARE OF UNCERTAIN ETIOLOGY..

Specimen(s) Received
LEFT CERVICAL LYMPH NODE

ANGIOTENSIN CONVERTI... 303

FINAL DIAGNOSIS

LYMPH NODE, LEFT CERVICAL:
- NON-NECROTIZING GRANULOMATOUS LYMPHADENITIS, SEE COMMENT

Comment: H&E stained sections shows completely effaced lymph node architecture by non-necrotizing, hyalinized granulomas. Special stains AFB and GMS are negative for bacterial and fungal organisms. Immunophenotyping of this specimen by flow cytometry reveals a mixed lymphoid population of T-cells and B-cells. There is no evidence of a monotypic B-cell population or T cell abnormality based on the markers assayed. These morphologic findings are compatible with sarcoidosis in the correct clinical context. The case was also

UCMC Clinical Course

- The patient was given aggressive IV fluid hydration with improvement in serum calcium 15.4→12.5
- Given that he was asymptomatic without EKG changes, calcitonin was deferred

Calcium	8.4 - 10.2 mg/dL	15.4 (HH)	14.4 (HH)	13.6 (HH)	14.3 (HH)	12.5 (H)	11.5 (H)	12.2 (H)	12.4 (H)
			IV fluids started	admitted		Prednisone 10mg	Prednisone 40mg + azathioprine		
		12.1 (H)	12.8 (H)	11.3 (H)	11.6 (H)	11.6 (H)			
				Prednisone switched to IV hydrocortisone					

Patient was discharged on azathioprine and prednisone 20mg with nephrology and rheumatology follow up

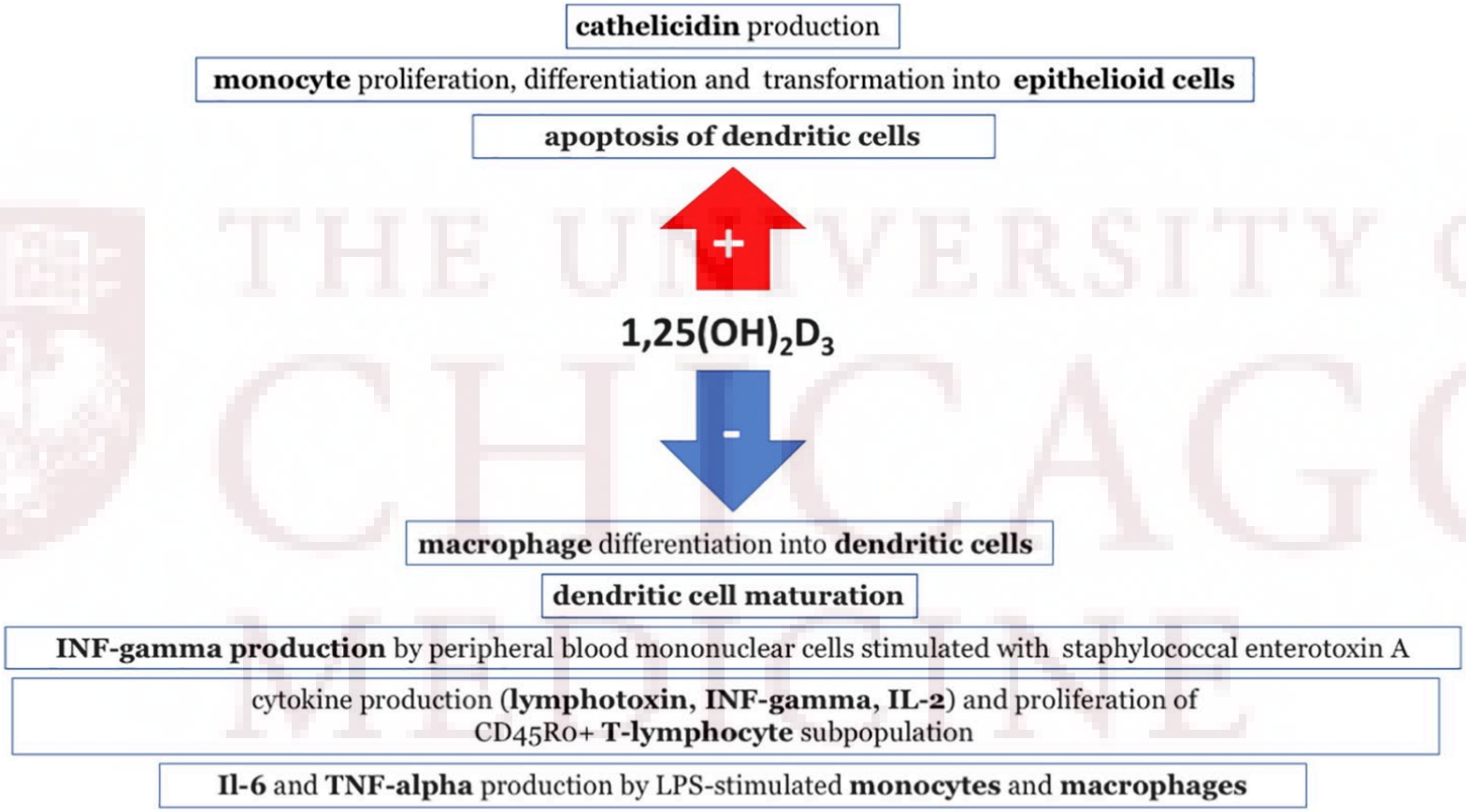
Endocrine Complications of Granulomatous Disease

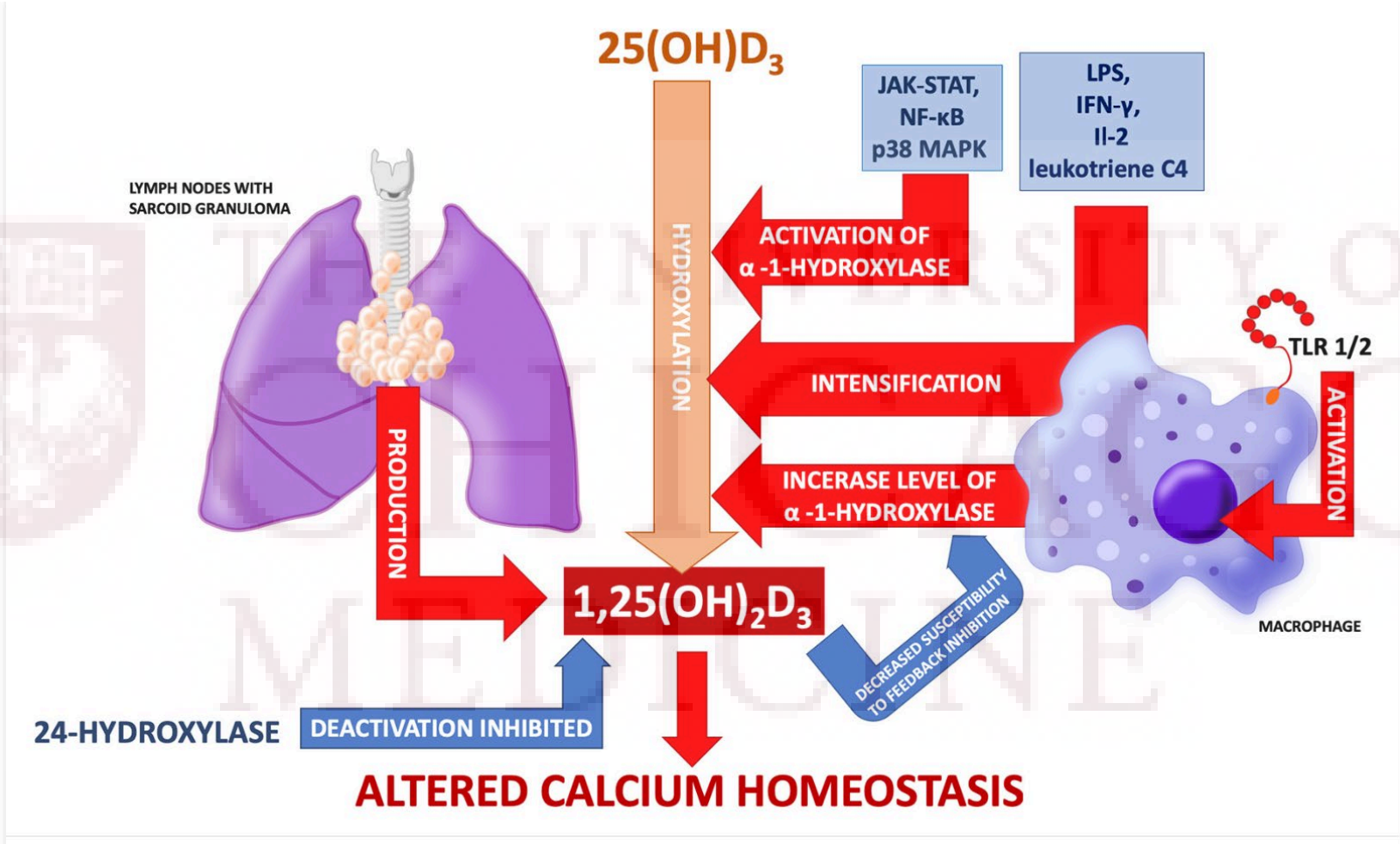
- Direct depositional disease (thyroid, adrenal, pituitary)
- Sarcoidosis and TB most common granulomatous causes of hyeprcalcemia
- Responsible for ~50% of Vitamin D mediated hypercalcemia, present in ~6% of all sarcoidosis patients
  - Hypercalcemia in anephric patients with sarcoidosis.
  - In vitro macrophage conversion of calcidiol to calcitriol from lymph node tissue from sarcoidosis patients
  - Elevated production of the mRNA from CYP27B1 (1-alpha hydroxylase) from alveolar macrophages from hypercalcemic sarcoidosis patients

Evidence that Increased Circulating 1_{α},25-Dihydroxyvitamin D is the Probable Cause for Abnormal Calcium Metabolism in Sarcoidosis

Norman H. Bell, Paula H. Stern, Elizabeth Pantzer, Tushar K. Sinha, and Hector F. Deluca

Published July 1, 1979 - More info


cathelicidin production
monocyte proliferation, differentiation and transformation into **epithelioid cells**
apoptosis of dendritic cells
+
$1,25(OH)_2D_3$
-
macrophage differentiation into **dendritic cells**
dendritic cell maturation
INF-gamma production by peripheral blood mononuclear cells stimulated with staphylococcal enterotoxin A
cytokine production (**lymphotoxin, INF-gamma, IL-2**) and proliferation of CD45R0+ **T-lymphocyte** subpopulation
Il-6 and **TNF-alpha** production by LPS-stimulated **monocytes** and **macrophages**


25(OH)D3
JAK-STAT,
NF-κB
p38 MAPK
LPS,
IFN-γ,
Il-2
leukotriene C4
LYMPH NODES WITH
SARCOID GRANULOMA
HYDROXYLATION
ACTIVATION OF
α -1-HYDROXYLASE
INTENSIFICATION
INCERASE LEVEL OF
α -1-HYDROXYLASE
TLR 1/2
ACTIVATION
PRODUCTION
1,25(OH)2D3
DECREASED SUSCEPTIBILITY
TO FEEDBACK INHIBITION
MACROPHAGE
24-HYDROXYLASE
DEACTIVATION INHIBITED
ALTERED CALCIUM HOMEOSTASIS

Management

- Reduce calcium intake (400mg/day)
- Reduce oxalate intake
- Avoid Vitamin D supplementation
- Reduce sun exposure
- IV hydration
- Steroids
- Loop diuretics
- Ketoconazole
- Hydroxychloroquine

Recommendation 5: In adults with hypercalcemia of malignancy (HCM) from tumors associated with high calcitriol levels, such as lymphomas, who are already receiving glucocorticoid therapy but who continue to have severe or symptomatic hypercalcemia, we suggest the addition of an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an IV BP or Dmab. (2⊕◯◯◯)

Glucose, Ser/Plasma	60 - 99 mg/dL	99
Sodium	135 - 145 mmol/L	141
Potassium	3.5 - 5.0 mmol/L	4.1
Chloride	98 - 108 mmol/L	105
Carbon Dioxide	23 - 30 mmol/L	26
Anion Gap	6 - 15 mmol/L	10
BUN	7 - 20 mg/dL	**29 (H)**
Creatinine	0.50 - 1.40 mg/dL	**2.02 (H)**
eGFR, All	>=90 mL/min/1.73 sq. m	**38 (L)**
Calcium	8.4 - 10.2 mg/dL	**11.9 (H)**

- Following with rheumatology and nephrology
- Continues on prednisone, azathioprine, low calcium diet
- If calcium is persistently elevated, rheumatology considering increased steroids vs adding ketoconazole

References

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