Hypercalcemia Secondary to Calcitriol and PTHrP Cosecretion Only Responsive to Hydroxychloroquine

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Learning Objectives

- Review etiologies of hypercalcemia of malignancy
- Review common therapies for hypercalcemia of malignancy
- Explore variations in the presentation of hypercalcemia
- Explore use of hydroxychloroquine in calcitriol-mediated hypercalcemia

Background

- Lymphoma-related hypercalcemia is most commonly associated with extrarenal calcitriol production
- Concurrent elevations in calcitriol and PTHrP levels are a rarely reported phenomenon previously described only in solid malignancies
  - Renal cell carcinoma[1]
  - Seminoma[2]
  - Colorectal cancer[3]
  - Squamous cell lung cancer[4]
  - Cholangiocarcinoma[5]
- Glucocorticoids are preferred therapy for calcitriol-mediated hypercalcemia to decrease calcitriol production and antagonize calcium absorption
- Second-line therapy for calcitriol-mediated hypercalcemia is classically ketoconazole
- Hydroxychloroquine has noted efficacy in calcitriol-medicated hypercalcemia of sarcoidosis, possibly from anti-inflammatory effects; however, it was unsuccessful when trialed in a single case of lymphoma[6]

Table 1: Hypercalcemia of Malignancy Review

Mechanism[7]	Associations	Medical Therapy
PTHrP (humoral hypercalcemia of malignancy [HHM])	Variable; squamous cell carcinomas	Anti-resorptive therapy
Osteolytic excess	Breast cancer, myeloma	Anti-resorptive therapy
Calcitriol	Lymphoma	Glucocorticoids
Ectopic PTH	Variable	Anti-resorptive therapy

Clinical Case

- 62 year-old female with diffuse large B cell lymphoma (DLBCL), progressive through multiple chemotherapy regimens, developed acute hypercalcemia ~5 years after diagnosis
- Work-up revealed elevated calcitriol with low PTH and PTHrP
- Zolendronate rapidly normalized calcium; upon hypercalcemia recurrence months later, repeat dosing was less efficacious and PTHrP was found to be newly elevated with continued rise in calcitriol levels
- Hypercalcemia persisted through high-dose glucocorticoids and denosumab until the addition of hydroxychloroquine, despite evidence of continued lymphoma progression

Case Timeline

7/2013: DLBCL diagnosis

7/2013-8/2017: R-CHOP with years of partial response until progression

11/2017-3/2018: disease progression through R-ICE, R-DHAP, R-gemcitabine

3/12/18-3/26/18: corrected calcium (**cCa**) rise from 9.9 → **11.6** mg/dL (8.9-10.3)

4/2/18: admission for large pulmonary embolus + **cCa 14.6**; treated with fluids + calcitonin

4/25/18: admission for **cCa 14.1**

4/26/18: **zolendronate** 4 mg IV

5/2018-9/2018: disease progression through ibrutinib & R-EPOCH; **high-dose glucocorticoids** x2

8/23/18: admission for neutropenic fever + **cCa 12.9**; treated with fluids + calcitonin

10/7/18: **zolendronate** 4 mg IV

10/5/18: admission for R-EPOCH; **cCa 11.7**

10/25/18: **pamidronate** 60 mg IV

10/20/18: admission for neutropenic fever; **cCa 11.9**; Endocrinology consulted; noted calcium intake of 1500 mg

11/7/18: **prednisone** 30→60 mg

11/12/18: **zolendronate** 4 mg IV

11/21/18-11/28/18: **denosumab** 120 mg IV weekly

11/7/18: admission for rituximab + venetoclax; **cCa 12.1**; cCa does not normalize and is 12.0 on discharge (nadir of **11.5**)

12/4/18: **dexamethasone** 3 mg IV→PO twice daily

12/5/18-12/24/18: **denosumab** 120 mg IV weekly

12/9/18: **hydroxychloroquine** 400 mg

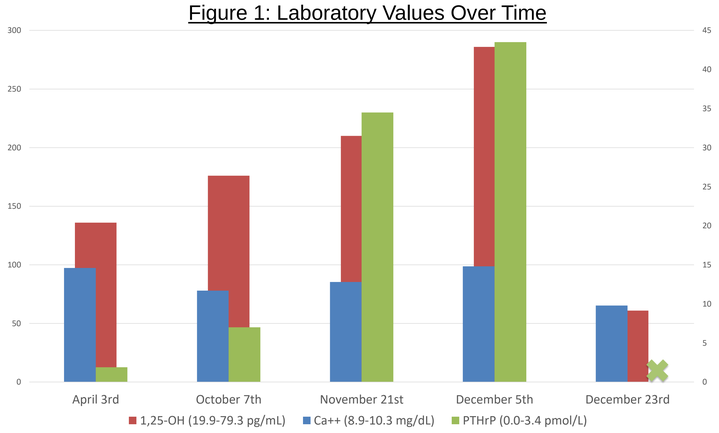
12/4/18: admission for **cCa 14.8**; ketoconazole contraindicated with venetoclax; **cCa** normalized for first time in 6 weeks and was **9.8** on discharge

1/16/19: **denosumab** 120 mg IV

1/8/19: admission for septic shock → hospice; **cCa 11.3**

Biochemical Trends

Figure 1: Laboratory Values Over Time



Discussion

- Hypercalcemia can be a presenting manifestation of malignancy but may also present years after diagnosis
- Depending on the type of cancer, hypercalcemia of malignancy may be classically associated with a specific etiology but can also be driven by more than one mechanism
- Decreased response to previously efficacious therapy should prompt reevaluation of hypercalcemia biomarkers as these can evolve over time
- Calcitriol and PTHrP cosecretion is rarely reported; this may be the first reported case (via PubMed search) to describe this phenomenon occurring with a hematologic malignancy
- Calcitriol and PTHrP cosecretion may require multiple therapies to antagonize different aspects of calcium metabolism
- Ketoconazole is associated with various drug interactions and poor patient tolerability
- Given potential for robust efficacy and favorable side effect profile, hydroxychloroquine should be considered in cases of calcitriol-mediated hypercalcemia resistant to glucocorticoids

References

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