Endorama: Denosumab-Induced Hypocalcemia
62-year-old gentleman with history of metastatic prostate cancer, with metastases to the dura, spine, and skull, status-post craniotomy, radiation, and chemotherapy

- Presents to the ER with weakness, diffuse numbness and tingling, particularly perioral and bilateral lower extremities, and a “jittery feeling”
History of Present Illness

- **Initial labs in ER:**
  
<table>
<thead>
<tr>
<th>141</th>
<th>106</th>
<th>13</th>
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<tbody>
<tr>
<td>4.2</td>
<td>19</td>
<td>0.9</td>
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  Ca 5.5  
  Mg 2.0  
  Phos 1.5  
  Ionized Ca: 2.84  
  Albumin: 3.7  
  Corrected Ca: 5.74  
  PTH: 227  

- QTc prolonged from 490 to 541ms within 12 hours of presentation.

- He was then given 2 doses of IV Ca gluconate 2g → Repeat BMP showed an ionized Ca of 2.76.

- The patient had his first Denosumab infusion 5 days prior to presentation.

- The Endocrinology service was consulted for assistance in further management of **hypocalcemia.**
Physical Exam

- **VS:** T 36.1; HR 104; BP 103/49; RR 20; O2 sat 100%; Wt 80.74kg; Ht 188cm
- **General:** Pleasant; cachectic-appearing
- **HEENT:** Normocephalic/atraumatic; dry MM; PERRLA; neck supple; no thyromegaly or lymphadenopathy
- **CV:** Regular rhythm; tachycardic; normal heart sounds; no murmurs/rubs/gallops
- **Pulm:** CTAB; no wheezes/rales
- **Abd:** Soft; NT/ND; normal bowel sounds
- **MSK:** Normal ROM; no edema or tenderness
- **Neuro:** AAOx3; patellar reflexes 3+ B/L; negative Chvostek’s sign
- **Skin:** Warm and dry; no rashes or erythema
- **Psych:** Normal mood and affect
Past Medical History

- **PMH**
  - Metastatic prostate cancer
  - Hypertension
  - Gout
- **Surgical History**
  - Craniotomy (4/2014)
- **Family History**
  - Not on file
- **Social History**
  - Widowed
  - Former smoker
  - Denies EtOH, illicits

**Medications**

- Abiraterone
- Allopurinol
- Calcium carbonate 500mg + Vitamin D3 BID
- Famotidine
- Ferrous sulfate
- Hydromorphone
- Levetiracetam
- Nifedipine
- Prednisone
- Peri-colace
- Tamsulosin
2006: Diagnosed with prostate cancer → Treated with radiation
2012: Admitted to OSH with osseous metastatic disease → Treated with Lupron and Casodex
3/2014: Dural metastases found on MRI, with diffuse expansion and heterogeneity of calvarial bones → Surgical resection and XRT
4/2014: Treated with prednisone and abiraterone as tertiary hormonal therapy
8/2014: Started on Docetaxel therapy due to rising PSA (and thus progressive disease)
The Patient’s Past Bone Health
The Patient’s Past Bone Health

- Prior X-rays and MRI’s consistent with above results
- Took Ca 500mg and Vitamin D twice daily (exact dose of Vitamin D unknown)
- OSH DEXA scan consistent with **osteopenia** with extensive bone metastases
- Patient received one dose of **Denosumab 120mg** based on these results
Bony Metastases in Prostate Cancer

- Predominantly osteoblastic, but analysis of bone turnover markers show that excess osteoclastic activity induces bone destruction
  - RANKL: Main driver of osteoclast formation, function, and survival
  - Osteoblasts produce up-regulation of RANKL, and down-regulation of RANKL inhibitor OPG (osteoprotegerin)
  - Inhibition of RANKL decreases sclerotic changes in the bone
Denosumab (Prolia, XGEVA)

- Human monoclonal antibody against RANKL → inhibits osteoclast-mediated bone resorption
- Prolia – Approved for use in post-menopausal women with osteoporosis
  ○ Dose: 60mg SQ every 6 months
- XGEVA – Approved for use in prevention of skeletal-related events in patients with bone metastases from solid tumors
  ○ Dose: 120mg SQ monthly
- In Phase 3 RCT’s, denosumab has been shown to significantly delay the time to first skeletal-related event compared with zolendronic acid
  ○ Greater suppression of bone-specific alkaline phosphatase and uNTx/Cr
- Hypocalcemia is a common side effect, often occurring in the first 6 months of treatment
Risk Factors for Hypocalcemia in This Population

- Prior treatment with bisphosphonate
- Presence of extensive osteoblastic metastases
- Potential malabsorption and GI loss of calcium from chemotherapy-induced diarrhea
- Renal impairment (eGFR <30 mL/min) (3,4)
Initial Work-Up and Management?
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- Ca gluconate IV pushes → The patient initially received 4g
  - Ca: 5.5 → 5.3
- Due to lack of response from Ca gluconate IVP, IV Ca drip was started at 1g/hour
- Calcitriol 0.25mcg PO BID was initiated
- 25-OH-Vitamin D and 1,25-Vitamin D levels were checked, and the patient was treated with an empiric dose of Vitamin D 50,000 IU
- Patient was started on PRN Neutraphos for hypophosphatemia
Our Patient

- 25-OH-Vitamin D: 14 ng/mL
- 1,25-Dihydroxy-Vitamin D: 154 pg/mL
Hospital Course

- Multiple futile attempts to wean off Ca drip
- Given the slow response of Ca, Calcitriol was increased to 0.50 mcg BID
  - By the time of discharge, in order to wean off Ca drip, Calcitriol was increased to 2.5 mcg BID
  - The patient is now on Calcitriol 1.0 mcg BID
- Daily Ca carbonate was added in addition to Ca drip
  - Increased from 500mg BID to 2500mg QID upon discharge
- Vitamin D3 supplementation was increased from 1000 IU daily to 4000 IU daily upon discharge
  - The patient also received 50,000 IU weekly for 3 weeks
Clinical Questions

HOW LONG IS HYPOCALCEMIA EXPECTED TO PERSIST IN A PATIENT WHO HAS RECEIVED DENOSUMAB?

WHAT IS THE MOST EFFICIENT WAY TO CORRECT PROLONGED HYPOCALCEMIA?
Hormonal Response to Hypocalcemia

- ↓ Plasma Ca²⁺
- ↑ PTH
- ↑ Calcitriol

- ↑ Calcium from bone
- ↑ Calcium from intestine
- ↑ Phosphate from bone and intestine
- ↑ Phosphate excretion in urine

- Increased plasma calcium
- Plasma phosphate unchanged
XGEVA Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XGEVA® safely and effectively. See full prescribing information for XGEVA.

Xgeva (denosumab)
injection, for subcutaneous use
Initial U.S. Approval: 2010

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia [see Warnings and Precautions (5.3)].

5.3 Hypocalcemia

Xgeva can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct pre-existing hypocalcemia prior to Xgeva treatment. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when Xgeva is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare professional for symptoms of hypocalcemia [see Contraindications (4.1), Adverse Reactions (6.1, 6.2), and Patient Counseling Information (17)].

An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake [see Adverse Reactions (6.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)].
How do we treat prolonged hypocalcemia?

- Very few case reports available of such resistant hypocalcemia
How do we treat prolonged hypocalcemia?

- In patients with normal renal function, hypocalcemia can be treated with a combination of oral and IV calcium with Vitamin D (1)
- In patients who are already on dialysis, hypocalcemia can be treated with a high calcium bath with Vitamin D supplement (1)
Back to Our Patient

- After a 3-week inpatient stay, follow-up Ca levels:
  - $7.1 \rightarrow 8.5 \rightarrow 7.7 \rightarrow 7.4 \rightarrow 8.3 \rightarrow 7.5$
  - Most recent corrected Ca: 7.34 mg/dL
- Repeat 25-OH-Vitamin D: 41
- Repeat PTH: 213
Conclusions

- It is very important to check both Ca and 25-OH-Vitamin D levels prior to starting treatment with denosumab.
- Increased risk factors for hypocalcemia following denosumab include: patients with osteoblastic metastases, prior bisphosphonate use, GI disease, and renal impairment.
- Patients should be maintained on low doses of PO calcium and Vitamin D while getting denosumab:
  - Prophylactic doses: Ca 500mg daily and Vitamin D 400 IU daily.
  - However, this may be inadequate in preventing hypocalcemia in some patients (such as ours).


