ONCOGENIC OSTEOMALACIA

THE SEARCH, THE TREATMENT, AND THE CURE OF A DEBILITATING TUMOR

NEW ENGLAND AACE ANNUAL MEETING

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Disclosures

• No financial or other conflicts of interest to disclose
Objectives

• Recognize the clinical features of patients with oncogenic osteomalacia

• Describe the role of FGF23 in the pathophysiology of the disease

• Understand an algorithmic approach to diagnosis and treatment of oncogenic osteomalacia
Case Presentation

- 48 year-old Haitian man presented to the hospital with several months of increasing lower back pain, debilitating fatigue, and progressive weakness of all four extremities

- Acetaminophen, gabapentin, muscle relaxants provided no relief
- Physical therapy provided mild relief
- Denied any glucocorticoid use in the past

- Review of Systems:
  - Endorsed diffuse joint and bone pains
  - No fevers, chills, headaches, hearing difficulties, weight loss, change in libido, or history of kidney stones
Case Presentation

- **PMH:**
  - L1-L3 laminectomy in Haiti 3 years prior (for unclear reasons)
  - Post-surgery, he had initially been dependent on crutches and has had progressive muscle weakness to the point he is now wheelchair dependent

- **Medications:**
  - Acetaminophen prn
  - Cyclobenzaprine prn

- **Allergies:**
  - None

- **Family History:**
  - No thyroid disease, autoimmune disorders, or disorders of bone metabolism

- **Social History:**
  - Single
  - Non-smoker
  - No children
Physical Exam

• General: Sitting in wheelchair. NAD. A&Ox3.
• HEENT: EOMI. PERRL. No stare or lid lag. MMM. Temporal wasting.
• Thyroid: Normal size, soft, non-tender. No nodules.
• Chest: Pectus excavatum.
• CV: RRR. Normal S1, S2. No murmurs.
• Lungs: CTAB.
• Abdomen: Soft. NT/ND. +BS.
• Skin: No rashes. Warm skin.
• Neuro:
  • CN II – XII intact.
  • 2/5 RLE, 3/5 LLE, 4/5 UE bilaterally. 2+ reflexes throughout. Toes downgoing.
  • Unable to stand up from wheelchair on his own. With assistance onto crutches, he displayed an antalgic gait.
## Admission Lab Studies

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>4</td>
<td>2.5 - 5 g/dL</td>
</tr>
<tr>
<td>Total Protein</td>
<td>7.2</td>
<td>6.8 – 8.6 g/dL</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>0.5</td>
<td>0.3 – 1.2 mg/dL</td>
</tr>
<tr>
<td>ALT</td>
<td>22</td>
<td>9 – 67 u/L</td>
</tr>
<tr>
<td>AST</td>
<td>28</td>
<td>13 – 39 u/L</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>599</td>
<td>25 – 100 u/L</td>
</tr>
<tr>
<td>Gamma Glutamyl Transferase (GGT)</td>
<td>39</td>
<td>11 – 58 u/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>9</td>
<td>8 – 10.5 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.4</td>
<td>2.7 – 4.5 mg/dL</td>
</tr>
</tbody>
</table>

CBC and BMP normal
Admission Imaging

L/S-spine X-rays: Vertebral body height loss.

T2-weighted MRI L/S-spine: Diffuse loss of vertebral height.
CT Chest/Abdomen/Pelvis with Contrast

Multiple insufficiency fractures seen involving the sacrum, bilateral iliac bones, ribs, and right scapula.
### Additional Lab Studies

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<tr>
<th>Lab</th>
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<tbody>
<tr>
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<td>18</td>
<td>30 – 60 ng/dL</td>
</tr>
<tr>
<td>1,25(OH)_2 Vit D</td>
<td>16</td>
<td>18 – 72 pg/mL</td>
</tr>
<tr>
<td>iPTH</td>
<td>136</td>
<td>11 – 90 pg/mL</td>
</tr>
<tr>
<td>FePh</td>
<td>26</td>
<td>10 – 20%</td>
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<tr>
<td>Creatinine</td>
<td>0.74</td>
<td>0.7 – 1.3 mg/dL</td>
</tr>
<tr>
<td>TSH</td>
<td>0.74</td>
<td>0.35 – 4.9 uIU/mL</td>
</tr>
</tbody>
</table>

SPEP/UPEP normal
FGF23 sent, but pending
Bone Scan

1) Increased uptake surrounding multiple joints, generalized uptake in the spine, and uptake of the bilateral costochondral junctions with a beaded appearance.

2) Focal uptake in the right mandible and left foot.
Mandible: No trabecular coarsening or distortion of the mandible.

Left foot: Non-displaced fractures of the bases of the third and fourth metatarsals.
MRI Left foot

**IMPRESSION:**
1. Multifocal stress fractures and stress reaction involving the calcaneal body, distal tibial metaphysis, talar dome, and second through fifth metatarsals, as detailed above.

2. No focally aggressive underlying bone lesion or soft tissue mass.
Hospital Course

- Patient was started on:
  - Ergocalciferol 50,000 international units weekly
  - Calcitriol 0.25 mcg twice daily
  - Calcium carbonate 1250 mg twice daily
  - Sodium phosphate 250 mg four times daily

- Discharged by medicine team with plans for outpatient endocrinology follow-up

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<td>277</td>
<td>&lt; 180 RU/mL</td>
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Diagnosis: Oncogenic Osteomalacia
Discussion
Oncogenic Osteomalacia

• AKA tumor-induced osteomalacia (TIO) or oncogenic hypophosphatemic osteomalacia

• Rare paraneoplastic syndrome resulting in renal phosphorus wasting, decreased intestinal phosphorus absorption, and decreased bone mineralization

• Signs/symptoms: progressive MSK pain, profound muscle weakness, and fractures

• Usually caused by small, slow-growing tumors of mesenchymal origin (70-80%), hemangiopericytomas, osteosarcomas, or giant cell tumors
  • Mesenchymal tumors
    • Phosphaturic mesenchymal tumor mixed connective tissue variant (PMTMCT)
Phosphaturic Mesenchymal Tumor Mixed Connective Tissue Variant (PMTMCT)

- Rare neoplasms
  - 53% of cases within bones
  - 45% in soft tissue
  - 3% in skin
- Usually benign, but malignant variants have been described
- Typical microscopic appearance of a PMTMCT is that of a highly vascular proliferation of spindled to stellate cells with low nuclear grade and low mitotic activity

Oncoengenic Osteomalacia

Dr. Robert Alexander McCance

Dr. Andrea Prader
Oncogenic Osteomalacia

- Tumors in oncogenic osteomalacia overexpress the protein fibroblast growth factor-23 (FGF23)

- FGF23 plays a key role in the control of serum phosphate concentrations
  - Maintains normal serum phosphate concentration:
    1) Inhibiting PTH secretion
    2) Reducing intestinal phosphate absorption
    3) Reducing renal phosphate reabsorption

- FGF23 is secreted by bone osteocytes and osteoblasts in response to calcitriol, increased dietary phosphate load, PTH, and calcium
Fibroblast Growth Factor-23 (FGF23)
FGF23 Effect on PTH

FGF23 Effect on Vitamin D

1) Decrease expression of 1α-hydroxylase

2) Increase expression of 24-hydroxylase

FGF23 Effect on Kidneys

- 70% of filtered phosphorus reabsorbed in the proximal tubules
  - Type 2 sodium-phosphate co-transporters (NaPi-IIa and NaPi-IIc) are the primary transport proteins responsible for phosphorus reabsorption in the kidneys

- In renal proximal tubular cells, FGF23 binds to the FGF receptor and its co-receptor, Klotho
  - Decreased expression of the NaPi-IIa and possibly also NaPi-IIc → renal phosphate wasting

# Oncogenic Osteomalacia

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>Characteristic findings</th>
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<tbody>
<tr>
<td>Phosphate</td>
<td>↓</td>
</tr>
<tr>
<td>Calcium</td>
<td>⇔</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (1,25-(OH)_2D)</td>
<td>⇔ or ↓</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (25-(OH)-D)</td>
<td>⇔</td>
</tr>
<tr>
<td>Parathormone</td>
<td>⇔</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>↑</td>
</tr>
<tr>
<td>FGF23</td>
<td>↑</td>
</tr>
<tr>
<td>Phosphate clearance (24-h urine sample)</td>
<td>↑</td>
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<tr>
<td>Fractional excretion of phosphate</td>
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Oncogenic Osteomalacia: Diagnosis

- Diagnosis is often challenging due to small tumor sizes (too small for detection by normal radiologic methods)

- Current recommendations to localize the tumor:
  - High-resolution magnetic resonance imaging (MRI) of the whole body
  - F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is a very sensitive method, but nonspecific
  - Octreotide scintigraphy (mesenchymal tumors often express somatostatin receptors)

Algorithm for Tumor Localization

Example of Venous Sampling

Example of Venous Sampling

Oncogenic Osteomalacia: Treatment

- Treatment of choice is complete, clear-margin resection of the causative tumor
- Prognosis is excellent following complete resection
- Abnormalities in phosphate wasting and vitamin D metabolism typically resolve within a few days following surgical intervention
- Clinical symptoms regularly resolve within a few weeks after surgery

Oncogenic Osteomalacia: Treatment

Oncogenic Osteomalacia: Treatment

Oncogenic Osteomalacia: Treatment

• In cases of incompletely resected tumors or unresectable tumors, radiotherapy is a therapeutic option of choice

• For tumors that cannot be located, medical treatment with phosphorus supplements and active vitamin D is required

Back to the Case

- Despite treatment with ergocalciferol, calcitriol, and phosphate supplementation
  - Phosphorus remained persistently < 2.0 mg/dL
  - Alkaline phosphatase increased to > 1000 u/L

- Octreotide Scan
Octreotide Scan

Single abnormal focus of increased uptake seen on planar imaging in the region of the right head seen on both 4 and 24 hour scans better localized on SPECT-CT to the right mandible. This correlates to the same focus of abnormal increased technetium HDP bone scan activity in the right angle of the mandible on the prior bone scan from 9/27/2016.
Maxillofacial CT without Contrast

1. Enhancing soft tissue measuring up to 1.8 cm in the right mandibular body corresponds to the region of abnormal uptake on the octreotide scan, which could represent the site of the primary tumor in this patient with suspected oncogenic osteomalacia.
In January 2017, the patient underwent biopsy of the right mandible lesion revealing fragments of vital woven and lamellar bone, as well as a focus of spindle cells of unknown significance.

- Segmental resection of right mandible
  - Pathology: Calcifying mesenchymal tumor

- Post-operatively, continued on ergocalciferol and calcium carbonate, but phosphorus supplementation and calcitriol were discontinued
  - POD1 FGF23 55 RU/mL (Reference Range: < 180 RU/mL)
## 1 Week Post-Op Labs

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Trending of Labs

<table>
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<tr>
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Clinical Improvement
Conclusions

- Oncogenic osteomalacia is a rare paraneoplastic syndrome resulting in hypophosphatemia and decreased bone mineralization due to increased FGF23 activity.

- Usually caused by small, slow-growing tumors of mesenchymal origin – often very difficult to localize.

- FGF23 decreases serum phosphorus concentration by:
  - Increasing urinary excretion
  - Decreasing intestinal absorption

- Patients usually cured by tumor resection with normalization of lab values and clinical improvement within weeks of surgery.
References


• McCance R. Osteomalacia with Looser’s nodes (Milkman’s syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. *Q J Med*. 1947;16(1):33-46.


Thank You!

Questions?
Comments?

Acknowledgments:
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