CME

Tumor-induced Osteomalacia (TIO): Diagnosis and Management

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Outline

• Describe clinical features of tumor induced osteomalacia
• Brief review of phosphate homeostasis
• Identify an approach to evaluation of the patient with hypophosphatemia
• Review management of the patient with tumor induced osteomalacia
Case Study

• A 70-year-old man presents for evaluation after feeling unwell for 7 years.
• He initially experienced right knee pain that progressed to bilateral knee, hip, and foot pain, as well as muscle weakness.
• He developed numerous stress fractures and ambulation became difficult.
• He eventually required a cane and electric scooter for mobility and was unable to perform many of the activities he was accustomed to—including dancing with his wife.

• Treatment for vitamin D deficiency did not resolve his pain and fractures.
• Many years after symptom onset, serum phosphorus was measured and the diagnosis of TIO considered.
Tumor Induced Osteomalacia

- Rare paraneoplastic condition characterized by chronic hypophosphatemia and osteomalacia
- Offending tumor can be found anywhere from head to toe
- Muscle weakness, bone pain and fractures are typical presenting symptoms
- Delay in diagnosis often for several years after onset of symptoms is common
- TIO is a curable disease

Salassa RM, et al. (1970) NEJM Vol 283(2)
Phosphate Homeostasis

Intake → Absorption → Extracellular Pool

Excretion → Formation → Resorption

NaPi 2b

Absorption → Reabsorption

Filtered

NaPi 2a
NaPi 2c

PTH
- Increase urine phos
- Increase 1,25(OH)₂D
- Bone resorption

FGF23
- Increase urine phos
- Decrease 1,25(OH)₂D

Urine Phosphorus excretion
Hypophosphatemia - Etiology

Not enough in...

Redistribution...

Too much out...
Not enough in...

- Low phosphorus intake
- Malabsorption
  - IBD, short bowel syndrome, chronic diarrhea
- Phosphate binders

Redistribution...

Shift to intracellular compartment
- Insulin therapy for DKA
- Acute respiratory alkalosis
- Refeeding syndrome

Phosphate uptake by bone
- Hungry bone syndrome (post-parathyroid surgery)
**Parathyroid mediated**
- Hyperparathyroidism
- Vitamin D deficiency
  - Nutritional, enzyme deficiency, VDR mutation

**FGF23 mediated**
- Tumor induced osteomalacia (TIO)
- X-linked hypophosphatemia (XLH)
- Iron infusions
- ADHR
- Fibrous dysplasia/McCune Albright syndrome
- Others

**Renal Proximal Tubule Defects (non-FGF23 mediated)**
- Renal Fanconi
- Sodium-phosphate transporter mutations
Low Serum Phosphorus

Assess urine phosphorus

Low Urine Phos (↑TmP/GFR)

Low/Non 1,25(OH)₂D
- FGF23 mediated

High PTH
- High 1,25(OH)₂D
- Non-FGF23 mediated

FGF23 mediated

High urine phos (↓TmP/GFR)

Normal PTH
- Low/NI 1,25(OH)₂D

Redistribution

High PTH
- PTH/Ca/Vit D disorder

Not enough in...
## Biochemical Findings of TIO

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphorus</td>
<td>Low</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>Normal</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Normal to slightly elevated</td>
</tr>
<tr>
<td>25-hydroxyvitamin D$_3$</td>
<td>Variable</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D$_3$</td>
<td>Normal or low</td>
</tr>
<tr>
<td>FGF-23</td>
<td>Normal or elevated</td>
</tr>
<tr>
<td>Urine phosphorus</td>
<td>Inappropriately high*</td>
</tr>
</tbody>
</table>

* Elevated fractional excretion of phosphorus or low TMP/GFR
Evaluation of the patient with TIO

**FGF23 mediated**
- Tumor induced osteomalacia (TIO)
- X-linked hypophosphatemia (XLH)
- Iron infusions
- ADHR
- Fibrous dysplasia/McCune Albright syndrome
- Others
Tumor Identification

- Careful physical examination – including skin
- Functional whole body imaging
  - $^{68}$Ga-Dotatate PET/CT
  - Octreotide scan
  - $^{18}$FDG PET/CT
  - Whole body sestamibi scan
- Anatomical imaging
  - CT
  - MRI
  - Ultrasound
- Venous Sampling (FGF-23 measurement)
  - Limited role if functional and anatomic imaging is negative

Breer S, (2014) Bone. Vol 64
Treatment Options

• Surgery
  • Treatment of choice when tumor is identified and can be resected

• Medical management
  • Phosphate and active vitamin D (calcitriol)
  • Anti-FGF23 antibody therapy
Phosphate and Calcitriol

Typical adult dose range

- Phosphorus: 500 – 2000+ mg/day in divided doses
- Calcitriol: 0.5 – 2 mcg per day

Too much phosphate
- Diarrhea
- Hypocalcemia
- Hyperparathyroidism
  - Secondary
  - Tertiary

Too much calcitriol
- Hypercalcemia
- Hypercalciuria
- Nephrocalcinosis
- Nephrolithiasis
Tumor Induced Osteomalacia
Normal Physiology

Tumor → Normal FGF23 → X → Phosphorus reabsorption
NaPi 2a NaPi 2c
Excess Phosphorus excretion

Anti-FGF-23 Antibody Therapy

Tumor $\rightarrow$ $\uparrow$ FGF23 $\rightarrow$ Crossed out $\rightarrow$ Kidney

- Phosphorus reabsorption
- NaPi 2a
- NaPi 2c
- Urine Phosphorus excretion

Key Take Away Points

• Tumor induced osteomalacia is a rare and often devastating condition

• **Measure serum phosphorus in patients with unexplained musculoskeletal complaints**

• Basic laboratory tests can determine cause of low phosphorus

• Tumor resection is curative

• If tumor is not found or not able to be removed, medical management can improve/resolve symptoms

• Keep looking if tumor not initially found!