A young man with hypertension, renal failure, hypercalcemia, and “no diagnosis”

Matt Ettleson, M.D.*

Endorama

October 24, 2019

M170
TELETYPING URGENT

TO: SAC, SAN FRANCISCO (9-2296)
FROM: DIRECTOR, FBI (9-49911)
UNSUB: "VALLEJO TIMES-HAROLD," VALLEJO, CALIFORNIA-VICTIM,
EXTORTION.

REURTEL NOVEMBER SIX LAST

LATENT FINGERPRINTS AND IMPRESSIONS THIS CASE NOT IDENTICAL
FINGERPRINTS OF [REDACTED] BORN [REDACTED] FBI NUMBER [REDACTED]

NO PALM PRINTS HERE FOR THESE INDIVIDUALS.

[REDACTED] AND [REDACTED] MAY BE IDENTICAL INDIVIDUALS NAMED RETEL.
NO FINGERPRINTS OUR FILES FOR [REDACTED]
Learning Objectives

• Briefly review the diagnosis and evaluation of independent hypercalcemia

• Explain the mechanism of hypercalcemia in sarcoidosis and other granulomatous diseases

• Discuss the fundamentals of adynamic bone disease

• Identify treatment options for hypercalcemia in sarcoidosis

• Speculate on role of hypercalcemia as a driver of renal failure in this case [if time allows]
22 year old man presents with headache, vision changes, and progressive lower extremity weakness.
HPI: a chronology

2007

Presents with abdominal pain, possibly appendicitis. An abdominal CT scan demonstrates borderline prominent mesenteric lymph nodes in the RLQ which is consistent with mesenteric adenitis. No secondary signs of appendicitis.

Abdominal pain resolved. No further work up at that time.
HPI: a chronology

2016

Presents with R inguinal pain. He has multiple palpable inguinal lymph nodes. He undergoes CT imaging, which demonstrates lymphadenopathy (again) and ascites.

calcium 12.8
albumin 4.2
protein 7.0
alk phos 61
AST 15
ALT 11
mag 2.1
LDH 128
PTH 1.2
Elevated serum calcium

Check repeat (total calcium corrected for albumin or ionized calcium)

Hypercalcemia confirmed by repeat measurement

Measure intact PTH

Elevated

Primary hyperparathyroidism

Mid to upper normal or minimally elevated

Primary hyperparathyroidism likely, consider FHH

Low-normal or low

Non-PTH mediated hypercalcemia

Measure:
- PTHrp
- 1,25-dihydroxyvitamin D
- 25-hydroxyvitamin D

Is PTHrp elevated?

Yes

Humoral hypercalcemia of malignancy more likely

No

Is 1,25-dihydroxyvitamin D elevated?

“Diagnostic approach to hypercalcemia.” Uptodate.com
Diagnostic approach to hypercalcemia. Uptodate.com
HPI: a chronology

2016

Presents with R inguinal pain. He has multiple palpable inguinal lymph nodes. He undergoes CT imaging, which demonstrates lymphadenopathy (again) and ascites.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Calcium</td>
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<tr>
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<tr>
<td>Mag</td>
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<td>LDH</td>
<td>128</td>
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<tr>
<td>PTH</td>
<td>1.2</td>
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<tr>
<td>Vitamin D 25-OH</td>
<td>15.8</td>
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<tr>
<td>Vitamin D 1, 25-OH</td>
<td>68.5 (cr 1.6)</td>
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<tr>
<td>TSH</td>
<td>4.0</td>
</tr>
<tr>
<td>PTH-rp</td>
<td>3.1</td>
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<tr>
<td>SPEP</td>
<td>normal</td>
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SPEP: normal serum protein pattern, normal IF
HPI: a chronology

calculator 12.8
albumin 4.2
protein 7.0
alk phos 61
AST 15
ALT 11
mag 2.1
LDH 128

PTH 1.2

TSH 4.0
Vitamin D 1, 25-OH 68.5
Vitamin D 25-OH 15.8
PTH-rp: 3.1

How do you interpret these findings in the setting of the patient’s acute kidney injury?

What are your next steps?
PTH-rp is widely expressed in normal and malignant tissues.

Most labs screen for C-terminal PTH-rp levels because it is more stable, but clearance depends on GFR.

PTH-rp can be falsely elevated in patients with renal failure without malignancy.
Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment

Peter J. Tobben, Ravinder J. Singh, and Rajiv Kumar

Vitamin D-Mediated Hypercalcemia

I. Introduction
II. Vitamin D-Associated Hypercalcemia
   A. Vitamin D metabolism
   B. Prevalence and clinical manifestations of vitamin D-mediated hypercalcemia
   C. Hypercalcemia associated with excessive ingestion of vitamin D and active vitamin D metabolites/analogues
   D. Hypercalcemia associated with granulomatous disease
   E. Hypercalcemia associated with CYP24A1 mutations
III. Summary and Conclusions

Hypocalcemia is encountered in 0.2 to 4% of community-dwelling subjects and hospital patients (1-8). The incidence of hypercalcemia is dependent upon whether serum calcium measurements are performed in free-living subjects in a community (1), in a hospital population (2–4), or in patients seen in an emergency department (5, 6, 8). Causes of hypercalcemia are listed in Table 1. Cancer-associated hypercalcemia and primary hyperparathyroidism are the most frequent causes of hypercalcemia. Their relative frequency depends upon whether the diagnosis of hypercalcemia is made in a hospital setting (where cancer-associated hypercalcemia is more frequent) or within the context of an outpatient practice (where the diagnosis of primary hyperparathyroidism predominates) (9).

From a diagnostic and therapeutic perspective, it is useful to think of hypercalcemia as a PTH-dependent or PTH-independent process. Increases in PTH concentrations in association with hypercalcemia indicate the presence of primary (10–14), tertiary (15–28), and post-transplant hyperparathyroidism (1, 21, 25, 26, 28–38) or severe neonatal hyperparathyroidism (associated with homozygous mutations of the calcium-sensing receptor) (39–42).
### Table 2. Vitamin D-Associated Hypercalcemia

#### Exogenous Vitamin D Toxicity
- Administration of excessive amounts of vitamin D₂ or vitamin D₃
- Administration of excessive amounts of 25(OH)D₃
- Administration of excessive amounts of 1α,25(OH)₂D₃, other 1α-hydroxylated vitamin D analogs such as 1α(OH)D₃, paricalcitol, and doxercalciferol in the context of chronic renal failure, end-stage renal disease, and hemodialysis therapy

#### Excessive Production of Vitamin D Metabolites
- Congenital disorders: excessive production of 25(OH)D and 1,25(OH)₂D₃, e.g., in Williams-Beuren syndrome with mutations of the Williams Syndrome Transcription Factor
- Granulomatous disease: excessive production of 1,25(OH)₂D₃: sarcoidosis, tuberculosis, leprosy, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, candidiasis, cat-scratch disease, Pneumocystis jiroveci or P. carinii pneumonia, Mycobacterium avium complex, Wegener's granulomatosis, Crohn's disease, infantile sc fat necrosis, giant cell polyomyositis, berylliosis, silicone-induced granuloma, paraffin-induced granulomatosis, talc granuloma.
- Lymphomas and malignant lymphoproliferative disease: excessive production of 1,25(OH)₂D₃: lymphoma, non-Hodgkin lymphoma, lymphomatoid, granulomatosis, inflammatory myofibroblastic tumor, dysgerminoma

#### Mutations in Enzymes Associated With Vitamin D Metabolite Degradation
- Mutations of the CYP24A1 gene: reduced degradation of 1,25(OH)₂D₃: infantile and adult hypercalcemia
HPI: a chronology (continued)

Paracentesis: no evidence of infection, cytology ‘negative for malignancy’

Bone marrow biopsy and peripheral smear: unremarkable

Core lymph node biopsy: reactive lymphoid tissue, no evidence of malignancy, no evidence of acid fast organisms or fungal elements.
HPI: a chronology (continued)

2018 - 2019
Further evaluation of secondary hypertension and renal disease

24 hour urine calcium: **535 mg/24h**
24 hour urine volume: 5050 mL/24h
24 hour urine creatinine: 1899 mg/24h
24 hour urine protein: 303 mg/24h

PTH **1.4**
Aldosterone: 5.5
Renin: 28.4
Serum metanephrines: 0.11
Serum normetanephrines: 0.22

Renal ultrasound with doppler:
bilateral nephrolithiasis and mild hydronephrosis; normal renal peak systolic velocities and resistive indices

Echocardiogram:
Reduced systolic function, EF ~40%
started on dialysis, early 2019
The patient presents to [Image] for evaluation headache, renal disease and weakness.

HPI

The patient presents with 3 weeks of weakness, nausea and weight loss. He is having trouble walking and has been falling at home. He has symptoms of lightheadedness but no vertigo. During his last session of dialysis, he had transient loss of vision and headache. He had one episode of emesis and has some non-specific abdominal pain that is near his baseline. He was seen recently in the cardiology clinic to establish care for a new diagnosis of heart failure. He has lost 25lbs in the last 2 months and has little appetite. He has no history of passing kidney stones. He denies constipation. He denies heavy calcium intake.
Emergency department evaluation

Vitals
Temp: 36.8
Pulse: 87
RR: 19
BP: 149/73
SO₂: 99%

Physical Exam
- general: fatigued, does not engage in conversation
- PERRL, EOMI
- CTAB but decreased effort
- RRR. No murmur appreciated
- Tunneled catheter line in place with no skin changes
- Diffusely tender to palpation in abdomen, scaphoid abdomen
- 2+ peripheral pulses
- No costovertebral tenderness
- No obvious skin changes.
- Depressed mood. When directly asked, will answer questions appropriately
Emergency department evaluation

Current Medications
Amlodipine 10mg daily
Aspirin 81mg daily
B complex-vit C-folic acid daily
carvedilol 25mg BID
cholecalciferol 1000 units daily
Ferric citrate 420mg TID
hydralazine 25mg TID
isosorbide mononitrate 60mg daily
Biochemical evaluation

- Calcium: 12.2
- Albumin: 4.0
- Protein: 6.8
- Alk Phos: 55
- AST: 16
- ALT: 13
- Mag: 2.0
- Phos: 4.4
- PTH: 6
- TSH: 1.86
- 25-OH vitamin D: 60
- 1, 25-OH vitamin D: 191

What is the significance of low PTH and alk phos in the setting of chronic renal failure?
Typically, ESRD leads to decreased 1,25 – Vit D levels, causing hypocalcemia and secondary hyperparathyroidism. Our patient’s PTH is LOW.
Is this patient at risk of having adynamic bone disease?

Adynamic bone disease: “low or absent bone formation in conjunction with thin osteoid seams, decreased cellularity and minimal marrow fibrosis.”

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Adynamic bone disease: “low or absent bone formation in conjunction with thin osteoid seams, decreased cellularity and minimal marrow fibrosis.”

“The principal factor underlying adynamic bone disease is either oversuppression of PTH release or resistance of PTH actions on the bone.”

PTH suppression can occur via use of calcimimetic agents, calcium-based phosphate binders or relatively high doses of vitamin D analogs.

It is noted that patients with CKD and adynamic bone disease have relatively low PTH levels, which are usually still above the upper limit of normal.

“Adynamic bone disease associated with CKD.” Uptodate.com
What are the clinical features of adynamic bone disease and how is the diagnosis made?

Most patients are asymptomatic. If symptoms are present, the most common are:

- bone pain
- fractures
- hypercalcemia
- vascular calcification

“Adynamic bone disease associated with CKD.” Uptodate.com
What are the clinical features of adynamic bone disease and how is the diagnosis made?

Among dialysis patients, **PTH levels less than 100 pg/mL** are consistent with ABD, especially if hypercalcemia is present.

High levels of **bone specific alkaline phosphatase** (>20 ng/mL) make ABD very unlikely.

Definitive diagnosis is made on **bone biopsy**.

Our patient’s bone-specific alkaline phosphatase: **8.5 ug/L** (0 – 20 ug/L).
radiographic and cross sectional imaging
CT C/A/P: Prominent mediastinal, axillary, and supraclavicular lymph nodes, pleural effusions. Hepatosplenomegaly, extensive mesenteric and retroperitoneal adenopathy, nonobstructive bilateral nephrolithiasis.
Left inguinal lymph node 1, 2 and 3: lymph nodes with non-caseating granulomas. Comment: The findings support the clinical impression of sarcoidosis assuming that cultures are negative for infectious etiologies.
22 year old man presents with headache, vision changes, and progressive lower extremity weakness.

Final diagnosis: **SARCOIDOSIS**

Started on 20mg prednisone daily.
Stopped vitamin D supplementation.
Metabolism of 25-Hydroxyvitamin D₃ by Cultured Pulmonary Alveolar Macrophages in Sarcoidosis

JOHN S. ADAMS, O. P. SHARMA, MERCEDES A. GACAD, and FREDERICK R. SINGER,
Bone and Connective Tissue Laboratory, Orthopaedic Hospital, and
Department of Medicine, University of Southern California School of
Medicine, Los Angeles, California 90007

Sarcoid associated pulmonary macrophages convert 25-OH vitamin D to 1,25-OH vitamin D via a specific hydroxylase that is not inhibited by vitamin D or calcium.

The process operates in a PTH-independent manner.
Other treatments:
- Diet modification
- Ketoconazole (P450 inhibitor)

Table 3. Initial Therapy According to Organ and Clinical Status.*

<table>
<thead>
<tr>
<th>Organ</th>
<th>Clinical Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>Dyspnea plus FEV₁, FVC &lt;70%</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Cough, wheezing</td>
<td>Inhaled corticosteroid</td>
</tr>
<tr>
<td>Eyes</td>
<td>Anterior uveitis</td>
<td>Topical corticosteroid</td>
</tr>
<tr>
<td></td>
<td>Posterior uveitis</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td>Skin</td>
<td>Lupus pernio</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Plaques, nodules</td>
<td>Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day</td>
</tr>
<tr>
<td></td>
<td>Erythema nodosum</td>
<td>Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Cranial-nerve palsies</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Intracerebral involvement</td>
<td>Prednisone, 40 mg per day</td>
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<tr>
<td></td>
<td></td>
<td>Azathioprine, 150 mg/day</td>
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<tr>
<td></td>
<td></td>
<td>Hydroxychloroquine, 400 mg/day</td>
</tr>
<tr>
<td>Heart</td>
<td>Complete heart block</td>
<td>Pacemaker†</td>
</tr>
<tr>
<td></td>
<td>Ventricular fibrillation, tachycardia</td>
<td>AICD</td>
</tr>
<tr>
<td></td>
<td>Decreased LVEF (&lt;35%)</td>
<td>AICD; prednisone, 30–40 mg/day</td>
</tr>
<tr>
<td>Liver</td>
<td>Cholestatic hepatitis with constitutional symptoms</td>
<td>Prednisone, 20–40 mg/day</td>
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<tr>
<td></td>
<td></td>
<td>Ursodiol, 15 mg/kg of body weight per day</td>
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<tr>
<td>Joints and muscles</td>
<td>Arthralgias</td>
<td>NSAID</td>
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<td>Granulomatous arthritis</td>
<td>Prednisone, 20–40 mg/day</td>
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<td>Myositis, myopathy</td>
<td>Prednisone, 20–40 mg/day</td>
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<td>Hypercalciuria and hypercalcemia</td>
<td>Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day</td>
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Monitoring response and follow up?
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Hypercalcaemia due to sarcoidosis corrects with bisphosphonate treatment

Charles J. Gibbs and Munro Peacock

MRC Mineral Metabolism Unit, The General Infirmary, Leeds LS1 3EX, UK.

Figure 1 Biochemistry and components of hypercalcaemia during treatment with hydrocortisone (HC), low calcium diet and APD. The stippled areas represent normal ranges and the dotted lines indicate zero.
Is there a direct effect of hypercalcemia on the kidney that leads to loss of filtration?