THE CASE

August 2015

CC: nodules on my hands

HPI: 33yo Hispanic male with ESRD on HD (3 years, unknown etiology) via Left AVF, HTN, HFrEF (15%) p/w multiple nodules on his fingers. They began to form about 6 months ago. He did not have any pain up until one day before presentation. He noticed that his left ring finger became very painful, cold to touch and the color changed to a dark purple. No skin breakdown.

Case was discussed with his outpatient nephrologist, who stated that the patient had a long history of noncompliance with medications and dialysis sessions.
Medications:
- Cinacalcet 60 mg daily
- Carvedilol 12.5mg BID
- Calcium acetate 2 tabs TID
- Ferrous sulfate 325mg TID
- Furosemide 60mg BID
- Lisinopril 5mg daily
- Sevelamer 1600mg TID

Social hx: denies tobacco, etoh, drugs
Past surg: AVF placement
Family hx: no renal disease or heart disease
Allergies: NKDA
Vitals  98.0  133/78  76  98% on room air  
NAD, aaox3  
RRR, no gallops  
Clear to auscultation bilaterally  
Soft, nt/nd  
Right hand: multiple nontender, non erythematous nodules (from 1 cm to 2cm in size) on the index and middle finger  
Left Hand: multiple nodules on fingers similar to the right hand. Ring finger with reduced flexion due to pain. Reduced warmth and delayed capillary refill which resolved on later assessment  
LUE AVF +thril/bruit
## LABS

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<th>CBC</th>
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COURSE

Dermatology evaluation
• Concerned about the left 4th digit. Believed they were tophaceous gout with a possible atypical gout flare. Possible calcium deposition within the nodules.

Rheumatology evaluation
• “Aspiration of tophi revealed multiple intracellular needle shaped crystals”
• No mention of birefringence but did say this was a strange presentation (no past history and normal uric acid not consistent with tophaceous gout)
• He was started on colchicine

Renal plan
• Low Ca bath with dialysis, Na thiosulfate, parathyroidectomy evaluation

He was discharged the next day to outpatient follow up.
RE-ADMISSION

He was re-admitted in October 2015.

This time because he had an acute pain in his hand with a new discoloration on the dorsum of his left hand between the 1st and 2nd metacarpals.

He had been continued on cinacalcet and a few weeks ago it had been increased to 180mg daily.

He was supposed to be on sevelamer. No vitamin D analogs. On my med rec, he did mention taking phoslo.

He had been seen by ENT as an outpatient and was scheduled for a 3.5 parathyroidectomy on Nov 16.

On exam the new lesion was exquisitely tender.
## LAB TREND

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COURSE

Dermatology evaluation
- Concerned for an embolic event
- Considering biopsy (note states it would help the differential but “would not be likely to change treatment at this time”)

Rheumatology evaluation
- Offered more aspiration, patient refused because of pain

Initiated on daily dialysis (normal calcium bath, no Na thiosulfate) with significant improvement (nontender on palpation) in his pain on evaluation prior to his third consecutive day.

Parathyroidectomy scheduled for Monday 10/19
Calcific uremic arteriolopathy (CUA)

- Occurs in ESRD patients
  - Also has been described in non-uremic patients
    - Primary hyperparathyrodisim, cancer, alcoholic liver disease, connective tissue disease
- Vascular calcification leading to intimal fibrosis
- Thrombus formation
- Skin necrosis

EPIDEMIOLOGY

1 year mortality is 45-80% depending on whether it is ulcerated. Leading cause of death is sepsis.

Prevalence of 4% among the ESRD population

- Based on a single retrospective study of one HD unit.
- Included 242 patients. 10 patients developed CUA.
- Characteristics of those effected
  - On HD longer 80 months versus 20 months (p<0.0001)
  - Higher Ca (p=0.03) and higher Phos (p=0.001)
  - Higher CaxP products (81.5 versus 52.9, p=0.0004)
  - PTH (1496 v. 138, p<0.0001)
  - Alk phos (188 versus 89, p=0.0001)

PATHOPHYSIOLOGY OF VASCULAR CALCIFICATIONS

The mechanism of vascular calcification resulting in CUA is believed to be due to an imbalance of inhibitors and inducers.

- Inhibitors include fetuin A, osteoprotegerin, matrix Gla protein. The first two are suppressed due to the chronic inflammatory state of uremia. The third is a vitamin K dependent protein
- Inducers include osteopontin, bone morphogenic protein 4

The trigger is unknown but believed to be related to a chronic inflammatory state and abnormalities in the mineral metabolism system

Phosphate is absorbed into vascular smooth muscle cells (VSMC) via Na-phosphate cotransporter resulting in activation of transcription factors this results in a transformation into osteoblast-like cells. These cells express proteins that lead to local calcification (osteocalcin, bone sialoprotein, type 1 collagen and osteopontin) resulting in the disease state.

There is also apoptosis of VSMC cells leading to release of vesicles which can trigger further calcification in the arteriole wall.

The gold standard is a biopsy. Unfortunately biopsies can put the patient at risk of ulceration. The biopsy needs to be deep enough to reach the subcutaneous tissue.

Findings include

- Calcification of medium sized vessels
- Fibrosis of the intima
- Intravascular thrombi
a The patient's left leg, on admission, with edema and erythema but without subcutaneous plaques, ulcers or other focal lesions. b Histology of the skin biopsy shows concentric calcification of the media layer of small arteriolar vessels, subintimal fibrosis and, consequently, arterial occlusion (von Kossa stain; ×400). There were no signs of underlying vasculitis. c The necrotic area expanded considerably and reached a maximum of 220 mm two weeks after the skin biopsy.
SOME POSSIBLE TREATMENTS

Wound care, antibiotics if necessary.

Correct the underlying abnormalities such as calcium, phosphorus, PTH
  - Parathyroidectomy, Cinacalcet, phosphate binders

Sodium thiosulfate

More dialysis
Parathyroidectomy for calciphylaxis

Retrospective analysis from 1993 to 2001

35 patients, 23 underwent parathyroid resection

They were followed for a median of 26 months (2 to 90 months)

Surgical patients had an improvement in their calcium, phosphate and PTH values (P<0.05)

They also had a longer median overall survival (80 months) compared to nonsurgical patients (35 months). (P<0.001)

SURGERY V. MEDICAL THERAPY (CINACALCET NOT AVAILABLE YET)

Single center, retrospective

Between 1989 and 2000, there were 13 patients with pathological/clinical criteria of calciphylaxis

7 received medical therapy and 6 underwent parathyroidectomy

Median survival was longer among the surgical compared to medical patients (36 v. 3 months, $P=0.021$)

CINACALCET

Unfortunately there are only case reports available for the use of this drug in CUA.

Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial

- 3861 patients, randomly assigned
- Secondary hyperparathyroidism in ESRD
- Adverse events reports

18 of the placebo patients and 6 of the cinacalcet developed CUA (relative hazard ratio 0.31, P=0.014)

Cinacalcet-mechanism of action

- Binds to the calcium sensing receptor on the parathyroid gland. Leading to increased sensitivity to calcium.
- Leads to reduced PTH secretion, calcium and phosphorus levels.

Floege et al. The Effect of Cinacalcet on Calcific Uremic Arteriolopathy Events in Patients Receiving Hemodialysis: The EVOLVE Trial. CJASN 2015; 10(5): 800-7
172 patients from Fresenius medical care North America
Received STS for CUA between 2006 to 2009
85% completed treatment
Survey questionnaires were send to physicians. Patient-level outcomes were only available for 53 patients
- 26% of CUA resolved
- 18% markedly improved
- 28% improved
- 6% did not improve
- 21% unknown

Limitations: no control, no mention on what other therapy was performed.

Nigwekar et al., Sodium thiosulfate therapy for calcific uremic arteriolopathy. CJASN. 2013 Jul;8(7):1162-70
Retrospective review of medical records at 4 hospitals over a 5 year period.
14 patients received STS for calciphylaxis during this period.
There was improvement in pain and the lesions themselves
But the mortality was 71% with 50% in the first 6 months.
Limitations: no control, no mention of other therapies

STS

Mechanism of action—unknown

There has not been an animal model to evaluate CUA but data is available for vascular calcifications.

- Wistar rats underwent 5/6 nephrectomy
- Three weeks later, they received 1 dose of STS intraperitoneally.
- They compared uremic rats treated with thiosulfate to control and found that there was no histological evidence of aortic calcifications compared to 73% of untreated uremic rats (P<0.001)
- The calcium content of tissue from the aorta, heart, renal was reduced in the STS group (P<0.05)
- Urinary calcium excretion was elevated (P<0.05 at 60 minutes and P<0.01 at 120 minutes and 180 minutes)
- They found that gamma-carboxyglutamate (Gla) protein-a calcification inhibitor- was higher in STS treated compared to untreated uremic controls (P<0.05)

Human aortic VSMC were induced into osteoblast like cells using high phosphate medium.

They looked at the expression of bone morphogenetic protein 2 and core binding factor α-1 (inducers of calcification) and GLA (matrix GLA protein-MGP) (inhibitor)

They divided the cells into two groups

- STS 1 were treated with STS
- STS 2 was cultured in a medium containing high levels of phosphorus for 72 hours and then treated with STS
- They then separated each group into subgroups of normal (only STS 1), high phosphate, and three concentrations of STS.

Both STS 1 and STS 2 showed that

- mRNA expression of BMP-2 were elevated in the high level phosphate group compared to normal. However they were reduced in the STS group compared to high phosphate.
- GLA was reduced in high phosphate compared to normal. But elevated in STS-treated compared to high phosphate.

All values were P<0.05

THE END