Calciphylaxis in Hemodialysis Patients

Preethi Yerram MD, MS, FASN

February 27, 2016

Objectives

- Define Calciphylaxis
- Risk Factors/Pathophysiology
- Clinical presentation, Diagnosis
- Treatment

Selye’s Calciphylaxis

Sensitization to Calciphylaxis by Endogenous Parathyroid Hormone

HANS BILYE, GIULIO GABBIANI AND RALPH STREBEL

Ontario and de Chirurgie expéimentale, Université de Montréal, Montreal, Canada

Endocrinology 71, 554-1962
“Condition of hypersensitivity in which, during a critical period after sensitization by a specific calcifying factor (Vit D compounds, PTH) - topical treatment with certain challengers (egg white/yolk, metallic salts) causes an acute local calcinosis followed by inflammation and sclerosis.”

Calcific Uremic Arteriolopathy

- Histopathology of human lesions showed small vessel (upto 600 µm) medial calcification and intimal hypertrophy in association with panniculitis and small vessel thrombosis (not described in Selye's lesions)
- Frequently associated with renal dysfunction
- Hence the term Calcific Uremic Arteriolopathy (CUA) was proposed*


**Epidemiology**

- CUA is most commonly seen in patients with ESRD
- Can be seen in conditions other than ESRD - primary hyperparathyroidism, malignancy, connective tissue disorder, alcoholic liver disease – **Non-uremic Calciphylaxis**
- Reported prevalence of 4% in patients on hemodialysis, and 1.3-4.5 per 100 patient years in patients with ESRD
- Mortality rate 60-80% mainly due to sepsis

**Risk Factors**

- Female gender
- Diabetes mellitus
- Caucasian race
- Obesity
- CKD-ESRD
- Low serum albumin
- Secondary hyperparathyroidism
- Hyperphosphatemia
- Hypercalcemia
- Vitamin D supplementation
- Calcium-based phosphate binders
- Increased aluminium
- Dialysis vintage
- Elevated alkaline phosphatase
- Peritoneal dialysis
- Warfarin/Vitamin K deficiency
- Corticosteroids
- Iron
- Erythropoietin

**Non-Uremic Calciphylaxis**

See Table for causes of non-uremic calciphylaxis.

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td>16 (27.9)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Chemotherapy-induced protein C and K deficiency</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Cancer disease</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Osteomalacia treated with nonparathyroid calcium</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Vitamn D deficiency</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>CKD (not ESKD)</td>
<td>1 (2.8)</td>
</tr>
</tbody>
</table>
Pathophysiology

- Disruption in the complex interplay between factors that favor calcification and those that prevent precipitation of calcium and phosphate with development of pathologic calcification

Pathophysiology

- Vascular calcification (VC) was previously thought to be a passive process secondary to the effects of elevated calcium and phosphorus level
- In vitro research showed differentiation of vascular smooth muscle cells (VSMC) into osteoblast-like cells on exposure to high levels of calcium and phosphorus
- VSMC are then capable of calcification and produce bone specific genes
- Loss of inhibition of mineralization from depressed vascular protective mechanisms such as pyrophosphate, matrix Gla protein (MGP), Fetuin-A

Pathophysiology: The Warfarin Link

- MGP is dependent upon vitamin K mediated γ-carboxylation for activation, thus altering the balance of the calcification cascade and explaining this association
- May explain link between Warfarin use and CUA
- Reduces protein C and S levels → procoagulant state
Pathophysiology

- Activity of nuclear factor kappa B (NFkB) is increased during inflammatory states and atherosclerosis thereby resulting in osseous mineral loss and VC


Clinical Presentation

- Single/multiple excruciatingly painful lesions
- Early lesions appear as non-specific violaceous mottling / livedo reticularis / erythematous papules / plaques / nodules
- Proximal / distal lesions (more common)
- Proximal lesions involve fatty areas – buttocks, thighs, breasts, abdomen
- Lesions may ulcerate – associated with high morbidity and mortality
CUA - Early Lesions

Livedo reticularis
Indurated/nodular lesion


Patient 1

- 42 yo white female with CRT/allograft dysfunction, HTN, h/o subtotal parathyroidectomy, h/o hypercoagulability on coumadin presented with painful nodular/erythematous lesions, some with ulcerations on upper extremities, abdomen, back and buttocks
- CKD stage IV
  - On coumadin, prednisone, active vit D analogs, ca-based phos binders
  - Elevated phosphorus, iPTH

Patient 2

- 62 YO white male with ESRD on PD, DM, HTN, Obesity (BMI 41), Afib on coumadin therapy was initially diagnosed with ‘cellulitis’ of left leg. This progressed to ulceration with eschar formation.
- Normal Ca, elevated iPTH, phos
  - On Calcium–based phos binders, active Vit D analogs
Differential Diagnosis

- Cholesterol embolization
- Warfarin necrosis
- Vasculitis
- Cellulitis
- Early lesions of Nephrogenic systemic fibrosis

Diagnosis

- Typical clinical findings
- Plain radiography – can show arborization of vascular calcification within the dermis and subcutaneous tissue – net-like pattern of calcifications
- Triple phase bone scan can be a useful non-invasive test to diagnose CUA; may have a role in monitoring progress with treatment
- Skin biopsy (requires adequate subcutaneous tissue sample) is diagnostic but may initiate an ulcer
Treatment

- Not standardized and optimal treatment regimen unclear
- Recommendations based on pathophysiological considerations
- Multidisciplinary approach is key in the management of CUA

Treatment

- General Measures
- Wound management and pain control
- Improvement of hypoxia – hyperbaric oxygen therapy (HBOT)
- Calcium and phosphorus control
- Antioxidant/ Chelation of Calcium
- Anti-inflammatory
- Antithrombotic
General Measures

- Eliminate trigger factors - corticosteroids, parenteral iron therapy, warfarin, calcium-based phosphorus binders, vitamin D supplements, erythropoietin
- Intensive nutritional support
- Antibiotics
- Avoid local tissue trauma including subcutaneous injections

Wound Management

- Proper wound care to prevent nodules from becoming necrotizing and spreading of existing necrosis
- Once CUA progresses to necrotic ulcer phase, mortality risk is significantly increased ranging from 30% to 80%

Surgical debridement

- Has been associated with improved survival*
- However this approach to wound management remains controversial
- Some reports suggest improved outcomes with atraumatic wound (regular wound cleansing and dressing) management compared to surgical debridement particularly in cases when the wound is dry and non-infected

Sterile Maggot Debridement

- Sterile maggot debridement in CUA has been described in case reports*
- Option in patients who did not respond to, or those that are not candidates for surgical debridement
- Debridement of necrotic tissue by larval enzymes and potential antibacterial activity
- May be limited by pain, and effective pain management in essential

*Mason D and Best DS. Advances in chronic kidney disease. 17 (5), 2010

Hyperbaric Oxygen Therapy*

- Used in cases with delayed wound healing
- Increases oxygen delivery to ischemic and necrotic tissue aiding the healing process (facilitate growth factor production, neovascularization, fibroblast proliferation and collagen synthesis)
- Increases oxygen delivery enhancing neutrophilic bactericidal activity which is dependent on superoxide production from NADPH linked oxidases

*Coates TH and Rogers NM. Seminars in Dialysis, 23(1): 2010
Hyperbaric Oxygen Therapy*

- Optimal number of sessions required unknown, but case reports suggest 20-30 sessions
- Expensive, limited availability, increased pain after session
- Adverse events include development of seizures, worsening gangrene, death from ventricular arrhythmias

*Coates TH and Rogers NM. Seminars in Dialysis, 23(1): 2010

Calcium and phosphorus control

- Dialysis modification
- Avoid calcium-based phosphate binders, vitamin D
- Cinacalcet – Calcimimetic agent
- Parathyroidectomy

Dialysis modification (Ca & P control)

- Lowering dialysate Ca concentration
- Increasing dialysis time
- Switching from PD to HD
Cinacalcet (Ca & P control)

- Calcimimetic - decreases serum PTH, calcium, CaXP
- Increasing use - “medical parathyroidectomy”
- Reports of improvement in pain as early as 2 weeks and complete healing between 4-14 months

Parathyroidectomy (Ca & P control)

- Role is unclear, especially since the advent of calcimimetics capable of “medical parathyroidectomy”
- Should be considered in the presence of persistent hyperparathyroidism despite calcimimetic use
- Decreases calcium levels and possibly improve CUA lesions
- May cause severe postoperative hypocalcemia requiring aggressive replacement

Parathyroidectomy promotes wound healing and prolongs survival in patients with calciphylaxis from secondary hyperparathyroidism.

Girotto JA et al., Surgery 2001

*One study showed improved outcomes/resolution of CUA lesions with subtotal parathyroidectomy – before the era of calcimimetics/STS

**Retrospective study = 7/16 pts with CUA had parathyroidectomy

The median survival time for parathyroidectomy versus nonparathyroidectomy was 14.8 and 6.3 months (P = .22)
Parathyroidectomy

- Retrospective analysis of 35 pts – 23 pts (66%) underwent a parathyroid resection

- Surgical patients had a longer median overall survival (80 months) than nonsurgical patients (35 months) (P<.001)

Sodium Thiosulfate (STS)

- First successful use of IV STS in CUA described in 2005 by Cicone et al.

- Multiple case reports/ case series describing successful treatment of CUA with STS since
Mechanism of action of STS

- Thiosulfate forms highly soluble complexes with calcium, thereby reducing the likelihood of calcium phosphate precipitation
- The antioxidant properties of thiosulfate might help restore endothelial cell dysfunction and promote vasodilation but experimental evidence of this effect is lacking.
STS – Dosing & Side Effects

- 25 gm mixed in 100 ml of normal saline given IV over 30-60 mins at the end of dialysis 3 times per week
- Reported duration of therapy 6 wks- 34 months
- Common side effects – nausea, vomiting, headache, increased AG acidosis, increased sodium
- Need to be wary of bone loss with long term use

Intralesional STS

- 4 patients with biopsy proven CUA
- Intralesional STS 250 mg/ml diluted 1:1 with 1% lidocaine– led to complete healing of lesions
- Localized discomfort during injection
### Bisphosphonates

- Antiresorptive bisphosphonates known to inhibit osteoclastic activity and possess anti-inflammatory actions.
- Reduce local macrophage infiltration and activity including decreased secretion of proinflammatory cytokines, thus facilitating the healing of CUA lesions.
- Use of bisphosphonates to be considered in patients failing to respond to other therapeutic modalities.
- Case reports of successful use of IV pamidronate, PO etidronate.

### Tissue Plasminogen Activator (tPA)

- Low-dose tPA has been reported to be beneficial in a single case report with predominately distal calciphylaxis.
- This type of therapy seems logical since many cases of CUA are found to have concurrent obliterator thrombus formation in addition to the obliterator endovascular fibrosis in arterioles.
- Further studies are needed in order to properly evaluate this therapy.

* Sewell et al. Arch Dermatol. 2006;140:1045-1048

### Corticosteroids

- Systemic corticosteroid use is thought to be a risk factor for CUA.
- But one study* reported the successful use of prednisone in ESRD patients with non-ulcerating plaques.
- In 14 patients without ulcers and increased risk of infection, prednisone led to stabilization or improvement in 11.

*Fine A and Zacharias J. Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy. KI, 61, 2002
Treatment Outcomes

Patient 1

Before treatment
Treatment

- STS x 5 months
- HBOT
- Surgical debridement and aggressive wound care
- Cinacalcet
- Fosrenol, Renagel
- Discontinued warfarin

4 months later….

Patient 2
Treatment
- Switched from PD to HD
- STS x 2 months
- Wound care
- Cinacalcet
- Discontinued warfarin
- Pt's lesions progressed with deterioration of his overall condition. Expired 4 months after diagnosis

Summary
- CUA is a serious condition with high morbidity and mortality
- Multidisciplinary approach is key
- STS should be considered as first-line therapy in addition to aggressive wound management and calcium-phosphorus control
- Other therapies such as bisphosphonates, corticosteroids, low dose tPA may be tried if initial therapy fails
- Evolving role of Vitamin K supplementation
- High mortality despite treatment

Thank You!