“Calciphylaxis”
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Controversies in Pathogenesis, Diagnosis and Treatment

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

I do not have any relevant relationships with industry
I will be discussing off-label use of medications

PATHOPHYSIOLOGY

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RENAL OSTEODYSTROPHY

- 2/2 secondary & tertiary hyperparathyroidism 2/2 hyperphosphatemia & hypocalcaemia due to CKD
- Clinically:
  - Bone Resorption
  - Metastatic calcifications in soft tissue (skin & cartilage)
  - Dystrophic vascular deposits in medium-sized vessels, aorta and heart valves

**Small-vessel disease:**
- Arterioles
- Subcutaneous capillaries (<0.6 mm diameter)

**“Calciphylaxis”: Calcific Uremic Arteriolopathy**
- Progressive medial calcification
- Sub-intimal fibrosis & intimal hyperplasia
- Thrombotic vaso-occlusion
- Cutaneous necrosis
- Systemic disease?
  - Pulmonary and GI?
  - Myositis, neuropathy
  - Increased cardiovascular events

**Non-Uremic Calciphylaxis**
- Skin lesions morphologically identical to CUA
- Mortality rate 52%
  - Improving
- Risk factors:
  - Warfarin, Female gender, obesity, primary hyperparathyroidism, alcoholic liver disease, malignancy and connective tissue disease

**Calcification in Renal Disease**
- Factors other than Ca-Phos promote calcification in renal disease
  - Phosphate binders and cinacalcet (calcimimetic) do not prevent vascular calcification, CV events & mortality
  - Increased recognition of cases in patients without ESRD

1. Calcification of vascular smooth muscle cell(s) (VSMC)
   - NFKB-mediated: Increased Bone morphogenic protein (BMP) activity
   - Endothelial-mesenchynal transition (EMT)

2. Thrombotic occlusion of arteriole and capillary endothelial cells
   - Impaired blood flow in adipose rich-areas
   - Systemic hypercoagulability
     - Two recent studies (Mayo and Partners) with hypercoagulable states

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**WARFARIN AS RISK FACTOR FOR CALCIPHYLAXIS**

- Warfarin association
  - Increased risk in German and Japanese Registries and other studies
- MGP: activated through Vitamin K decarboxylation
  - Inhibits vascular calcification by inhibiting BMP-2
  - Inhibition might promote both calcification and thrombosis

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**CKD/VITAMIN K/MGP**

- HD patients: 4.5-fold higher of inactive uncarboxylated MGP
  - Correlates with vascular calcification in HD patients
- Low uncarb-MGP = increased all-cause & CV mortality
- Cirrhosis: Vitamin K deficiency 2/2 decreased bile salt synthesis and impaired absorption
### Calciphylaxis: History and Physical Exam

- **Symptoms:**
  - Active cutaneous disease:
    - Severe pain, induration, erythema
  - Morphologies depend on stage of disease:
    - Livedoid changes, panniculitis, bullae, stellate ulcers & eschar

- **Location:** Adipose-rich areas
  - Medial and lateral thighs
  - Calves
  - Buttocks
  - Abdominal pannus
  - Lower back
  - Breasts
  - Atypical areas in advanced disease: upper extremities, scalp, face

### Calciphylaxis Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>ESRD and HD</td>
<td>↑ RANKL, ↑TNF-α, ↓fetuin-A, high levels of inactive MGP</td>
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<tr>
<td>Hyperphosphatemia and Hypercalcemia</td>
<td>Less likely metastatic calcification and precipitation, ↓ NFkB</td>
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<tr>
<td>Alcoholic Liver Disease</td>
<td>IL-1 and TNF-α ↑ RANKL, ↓active MGP, ↓Protein C&amp;S, ↓Fetuin-A</td>
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<tr>
<td>Hyperparathyroidism</td>
<td>↑ RANKL, ↓OPG</td>
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<tr>
<td>Glucocorticoids</td>
<td>↑ RANKL, ↓OPG</td>
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<tr>
<td>Warfarin (Dietary Vitamin K deficiency)</td>
<td>↓ of Vitamin K-dependent MGP (Gastro bypass)</td>
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<td>Aluminum</td>
<td>↑ calpain, an inhibitor of NFkB inhibitory protein</td>
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<tr>
<td>Autoimmune disease and Inflammation</td>
<td>IL-1 and TNF-α ↑ RANKL upregulation, ↓fetuin-A</td>
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<td>Obesity</td>
<td>Chronic tension on septae and arterioles promotes dystrophic calcification, TNF-α</td>
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<td>Female Gender, Age&gt;50 (Menopause)</td>
<td>Estrogen: ↑OPG expression</td>
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<tr>
<td>Vitamin D analogues</td>
<td>↑ RANKL</td>
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Livedo Racemosa with central pallor and skin necrosis

Retiform-shape Eschar
**DISTAL/ACRAL CALCIPHYLAXIS**

- Less common presentation
- Acral necrosis and gangrene
  - Hands and fingers
  - Feet and toes
  - Penile
  - Vulvar (case reports)
- Can coexist with more typical disease

**DIFFERENTIAL DIAGNOSIS**
**WARFARIN SKIN NECROSIS**

- Clinically indistinguishable
  - Adipose-rich areas
- Presents within 10 days of initiation
- vs. warfarin-induced Calciphylaxis
  - After months or years of treatment
- Biopsy:
  - + subcutaneous thrombosis without calcification

**OTHER THROMBOTIC DISEASE**

- Antiphospholipid Antibody Syndrome
- HITT
- Cold-precipitating protein disease (Cryos)
- Peripheral vascular disease

**DIAGNOSIS**

- In a patient with ESRD presenting with a painful erythematous livedoid skin changes on adipose-rich areas
  - Diagnosis is Calciphylaxis unless proven otherwise

**Skin Biopsy?**

- Unknown/Low sensitivity and specificity
  - Limited depth of the specimen,
  - Biopsy site
  - Clinical stage at the time of biopsy
- Risk of poor wound healing and new lesion formation

**PRIMARILY A CLINICAL DIAGNOSIS**
HISTOPATHOLOGY OF CALCIPHYLAXIS

- Small-sized arteries and arterioles:
  - Medial calcification and intimal fibrosis

- Subcutaneous tissue:
  - Lobular capillary and arteriolar
  - Calcification
  - Thrombosis

BIOPSY FOR CALCIPHYLAXIS

- Retrospective review of the histopathologic findings in 56 biopsies from confirmed calciphylaxis:
  - Classic features: only 18% of samples

<table>
<thead>
<tr>
<th>Table 1. Histologic Features of Calciphylaxis Versus Noncalciphylaxis Controls</th>
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<tr>
<td></td>
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<tr>
<td>Calcium deposits</td>
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<tr>
<td>Vascular calcification</td>
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<tr>
<td>Intra-vascular calcification</td>
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<tr>
<td>Vascular changes</td>
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<tr>
<td>Vascular thrombosis</td>
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<tr>
<td>Eosinophilic infiltration</td>
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<tr>
<td>Neutrophilic infiltration</td>
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<tr>
<td>Subcutaneous changes</td>
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HISTOPATHOLOGY PITFALLS

- Non-inflammatory thrombosis may be only finding in early calciphylaxis
  - Present in 66-86% of cases.
  - Not specific to calciphylaxis
- Presence of both subcutaneous capillary thrombosis & calcification more specific
- Thrombosis (but not calcification) also seen in Warfarin-induced skin necrosis

If biopsy is performed....

- Is biopsy needed?
  - Lab evaluation may be adequate
  - More useful in non-uremic
- Adequate biopsy
  - 6-8 mm punch at edge with telescoping 4 mm down to fat
  - Wedge biopsy of surrounding skin, wound edge and base down to fat
- Experienced Dermatopathologist or Pathologist
- Von Kossa and Alizarin-red stains for peri-eccrine calcification may increase sensitivity

LABORATORY EVALUATION OF SUSPECTED CALCIPHYLAXIS

- Two major goals:
  - Assess for the presence of risk factors
  - Rule out other vasculopathic or vasculitic disorders

Hypercoagulability/Vasculitis workup

- Labs:
  - PTT, PT/INR, D-dimer, Fibrinogen, LDH
  - ANA, ENA, ANCA's (IF and ELISA)
  - Antiphospholipid antibodies
    - Lupus Anticoagulant
    - Anti-cardiolipin
    - Anti-b2-glycoprotein
    - Anti-phosphatidylyserine
- Labs:
  - SPEP/UPEP
  - Cryoglobulins & Cryofibrinogens, RF
  - Protein C&S, anti-thrombin III, Vitamin K
  - Possibly Factor V Leiden mutation
  - Possibly Prothrombin mutation
RENEAL FUNCTION/MINERAL BONE PARAMETERS EVALUATION

- BUN/Creatinine
- PTH, Vitamin D
- Serum Calcium and Phosphorus
  - Calcium-phosphorus product > 70 mg²/dL classic
  - Important to look back at all labs

STUDIES: ACRAL CALCIPHYLAXIS

- TTE or TEE:
  - Rule out embolic disease
- Vascular Studies:
  - ABI
  - Arterial duplex U/S or CT-A
  - Rule out “steal syndrome”
- Buerger’s disease:
  - Tobacco use
- Paraneoplastic vascular syndromes

ADDITIONAL IMAGING

- Bone Scan
  - Not currently recommended due to unclear sensitivity
- XR
- Mammogram technique
  - Lack of controls?

TREATMENT
No randomized controlled trials addressing proposed interventions
- Retrospective cohort studies, case report and series
- Expert opinion based on clinical experience and observational data

Some recommendations may run counter to standard medical practice and all meds are off-label
- Anticoagulants in patient with CKD and ESRD
- Bisphosphonates in patients with ESRD

Multidisciplinary care is key:
- Derm
- Renal
- Cardiology/Pulmonary/Hematology
- Hepatology
- Wound Care
- Pain Management/Palliative care
- PCP

Prognosis is grim:
- One-year survival rates: 45.8%
- Two-year survival rate: 20%
- Mortality increased at 1, 2, 5 years even when controlling for HD
- Proximal (above the knee) disease probably worse
- Combination of both distal and proximal disease worst
- Penile involvement: mortality rate of 69% within 6 months
**PROGNOSIS AND PALLIATIVE CARE**

- Early discussion with patients and families:
  - Prognosis
  - Approach to future therapy
    - Months not weeks
- Not uncommon to have patient stop HD 2/2 pain
- Referral to Palliative care

**PAIN CONTROL**

- Refer to Pain or Palliative care
- Challenging due to decreased renal clearance (Morphine)
- Narcotics
  - Baseline: Fentanyl patch
  - Breakthrough and Dressing changes: Hydrocodone, Hydromorphone (not renally cleared)
- Other adjunctive:
  - Gabapentin, Pregabalin
  - Lidocaine gel

**WOUND CARE AND DEBRIDEMENT**

- Recommendations:
  - Avoid trauma and debridement during active ischemic phase
    - SQ injections
  - Exception: Signs of active infection
  - Follow patient weekly
  - Refer to Wound Care clinic

**WOUND CARE AND DEBRIDEMENT**

- Inactive wound (no signs of ischemia):
  - Gentle debridement of eschar:
    - Hydrocolloid dressings (Duoderm®)
    - Medihoney
    - Q3-5 days
  - Atraumatic debridement methods:
    - Maggots debridement therapy
    - Water jet irrigation;
    - Ultrasonic assisted wound treatment (UAW)
MAGGOT DEBRIDEMENT THERAPY

- *Lucilia sericata*
- Debridement of necrotic tissue, stimulation of granulation tissue, antimicrobial effect
- Cost effective: $100 for 250 maggots from Monarch labs
- Performed at bedside over 48 hours
  - 2-4 cycles generally needed

WOUND CARE

- Hyperbaric oxygen
  - Limited by patient claustrophobia, access to treatment, and cost
  - Consider as second-line therapy

NUTRITION - CALCIPHYLAXIS

- Nutrition consult
- Malnutrition frequently present
  - Inhibits wound healing
  - Hypoalbuminemia associated with calciphylaxis
  - Vitamin K deficiency
- Gastric tube or parenteral nutrition.
MEDICAL MANAGEMENT

SODIUM THIOSULFATE (STS)

- Currently preferred treatment based on numerous case reports and case series
  - Multiple case series with "improvement"
  - Questionable mortality benefit
    - 1-year mortality in three studies (pts): 35% (172), 52% (27), 71% (14)
  - Mechanism: Unknown
    - Increases solubility of calcium and forms a dialyzable salt
    - Vasodilatory and antioxidant properties
    - Decrease in fetuin-CPP particles following treatment

SODIUM THIOSULFATE

- Preferred dosing:
  - 12.5-25 g intravenously in 100 mL of NS during last 30 min of HD BIW - TIW
  - Continued until lesions are healed
- Intralesional for isolated disease
  - Possibly effective for limited disease
  - Risk of worsening with Koebnerization and Trauma?

SODIUM THIOSULFATES: PITFALLS

- Side effects:
  - Nausea, headache, hypotension
    - Premedication
    - Start lower dose: 12.5 grams
    - Improvement with subsequent infusions
  - Rare side effects:
    - Severe metabolic gap acidosis
- Accessibility of treatment:
  - Obtaining medication and coordination with HD center
  - Cost: $10,000 per month
**HD MANAGEMENT**

- Nephrology optimizes to National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) goals of dialysis adequacy
- Intensive HD (i.e. increasing to 5X per week)
  - Unclear benefit
- Peritoneal dialysis:
  - Higher calciphylaxis risk vs HD?
  - Not standard practice to transition PD to HD
  - Avoid intraperitoneal STS (peritonitis and death)

**ANTICOAGULATION**

- Two questions:
  1. Is there an indication for full anticoagulation in all patients with calciphylaxis?
  2. Patients presenting with calciphylaxis already on warfarin for other indications?

**CKD–Mineral Bone Disease Axis Abnormalities**

- Non-calcium phosphorus binders: Sevelamer
- Serum PTH: 150-300 ng/mL
  - Cinacalcet: preferred treatment
  - Surgical parathyroidectomy: 2nd line
- Avoidance:
  - Calcium supplements
  - High dialysate calcium bath
  - Vitamin D preparations

**ARGUMENTS FOR ANTICOAGULATION IN ALL PATIENTS?**

- Thrombosis is a key feature in histopathology of calciphylaxis
- Non-uremic calciphylaxis
- Systemic hypercoagulable states
  - Likely increases risk for calciphylaxis
**ANTICOAGULATION IN ALL PATIENTS WITH CALCIPHYLAXIS?**
- Full long-term anticoagulation not currently recommended in patients without other underlying indication
  - Lack of safe options other than Warfarin
- Alternatives:
  - Pentoxifylline 400-800 mg po qday
    - Reduces blood viscosity
    - Decreases platelet aggregation and inhibits thrombus formation
    - Anti-inflammatory (anti-TNF) effect

**WARFARIN ALTERNATIVES IN PATIENTS REQUIRING LONG-TERM ANTICOAGULATION**
- Risk-Benefits:
  - Discussion with prescribing physician should focus on the following:
    - Calciphylaxis has high mortality (yearly) vs CVA prevention (over 5 years)
    - Growing awareness among nephrologists

**WARFARIN ALTERNATIVES IN PATIENTS REQUIRING LONG-TERM ANTICOAGULATION**
- No data whether discontinuation of warfarin improves outcomes
- Evaluate whether full anticoagulation still indicated
  - Provoked DVT’s (1 year)
  - Atrial Fibrillation in ESRD (possible lack of benefit)
- Tough cases:
  - Cardiac assist devices
  - Mechanical heart valves
  - Antiphospholipid antibody syndrome

**WARFARIN ALTERNATIVES IN PATIENTS REQUIRING LONG-TERM ANTICOAGULATION**
- Aspirin
- New target-specific oral anticoagulants:
  - Off-label in patients with CKD
    - Apixiban 5 mg po bid,
      - 2.5 mg bid: age >80 years or body weight <60 kg
  - Not approved for mechanical heart valves, cardiac assist devices, ?APLS
**WARFARIN ALTERNATIVES IN PATIENTS REQUIRING LONG-TERM ANTICOAGULATION**

- Inpatient admission for continuous IV heparin infusion
- LMWH with Factor Xa monitoring
- Full-intensity unfractionated subcutaneous heparin

**Bisphosphonates:**
- Pamidronate (30 mg qday x 3, repeated monthly) and Alendronate
- Alendronate 10 mg po qday, 70 mg po qweek

2nd line in ESRD - Typically contraindicated in severe renal impairment

Adjunctive 1st line in non-uremic calciphylaxis

**Denosumab:**
- Theoretical benefit through RANKL inhibition
- No case reports

**OTHER ADJUNCTS: VITAMIN K**

- **K1:** 30 mg per week
  - Cheaper OTC

- **K2 (menaquinone-7 [MK-7]):** 360-1080 µg TIW
  - K2 supplementation in patients on chronic HD decreases levels of uncarboxylated MGP

**Safety:** ? Thrombosis
  - No toxic dose exists
  - High doses have not been shown to increase clotting risk in mouse studies

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**RENSAL TRANSPLANTATION**

- Reports of both resolution of calciphylaxis and new onset of calciphylaxis after transplantation
  - Cytokine release related to surgery
  - Corticosteroids

Infection & poor wound healing 2/2 corticosteroids
COORDINATION OF CARE

- Patients often discharged with active thrombotic disease
  - Goals:
    - Initiation of STS and other treatments in hospital
    - Pain control

- Patients commonly discharged to LTAC or SNF
  - Difficulty in obtaining and paying for STS
  - Choice of LTAC and SNF with experience

SUMMARY

- Clinical diagnosis: In a patient with ESRD presenting with painful erythematous livedoid skin changes on adipose-rich areas
  - *Diagnosis is Calciphylaxis unless proven otherwise*

- Acral calciphylaxis difficult due to concomitant PVD

- If diagnosis is in question, biopsy can be performed after discussing risks and benefits
  - Specimen must contain fat
  - Should be read by experienced Dermatopathologist

- Non-uremic Calciphylaxis exists

- Currently favored treatment: Sodium thiosulfate 12-25 grams biw-tilw

- Consider:
  - Vitamin K supplementation (at least 35 mg per week), or K2 720 micrograms
  - Bisphosphonate for progressive disease or non-uremic calciphylaxis
  - Pentoxyfylline 400 mg po tid in non-uremic calciphylaxis

- Reevaluate need for Warfarin and other associated medications
  - Apixiban
  - Aspirin

- Avoid debridement during acute “thrombotic” phase unless visibly infected
Do not discharge patient until coordination of outpatient care occurs

End-of-life discussion
Sodium Thiosulfate procurement
Wound care plan
Nutrition
Pain control

Improvement generally takes many months

Disease can recur
Consider life-long Vitamin K supplementation

Multispecialty coordination is critical

REFERENCES


