Atypical Wounds: Calciphylaxis: A comprehensive overview of this Difficult Disease

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• None to disclose

• Recognition to my team:
  • Dr. David Truong, DPM
  • Dr. Marcus Riedhammer, MD
  • Rob Yordy, RN
  • Lora Nizinski, NP
  • Patient and patients family
The Art of Learning

The capacity to learn is a GIFT; the ability to learn is a SKILL; the willingness to learn is a CHOICE.
~ Brian Herbert

Live as if you were to die tomorrow. Learn as if you were to live forever.
~ Mahatma Gandhi
Objectives:

• **Review** the two types of Calciphylaxis and wound features

• **Recognize** key features related to both Calcific Uremic Arteriolopathy (CUA) vs Nonuremic Calciphylaxis (NUC)

• **Compare** treatment options and outcomes

• **Discuss** the importance of a team approach for best patient outcomes
Real life Objectives:

• Realize we don’t know it all
• We learn from each other
• Every patient/wound is an opportunity to learn & improve
• Don’t be afraid to do be wrong while doing the “right thing”
• Ask the questions and find the answers
• ALWAYS start with your BASICS
• Work systematically
Overview of Calciphylaxis

• First described in 1961 by Dr. Hans Selye et al. as a “systemic hypersensitivity reaction” where lab animals had calcification of various organs induced after exposure to:
  • one of several sensitizing agents aka “calcifiers” (i.e., Vit. D2, D3, Parathyroid hormone)
  • followed by exposure to a “challenger” (i.e., metallic salts (Fe, Al), egg albumin, and trauma)

• Years later, this was then seen primarily in uremic patients and therefore originally thought to be only associated with ESRD

• Histopathology is the gold standard in diagnosis with a clinical presentation and suspicion: pathology shows
  • small-vessel mural calcification
  • extravascular calcification and thrombosis leading to ischemia with skin and soft tissue necrosis
  • High mortality.
Two Types of Calciphylaxis

**Calcific Uremic Arteriolopathy (CUA)**
- Most prevalent
- Associated with ESRD
- ~4.1% incidence in patients undergoing hemodialysis
- Underlying mineral abnormalities
- High Mortality with leading cause of depth= sepsis

**Nonuremic Calciphylaxis (NUC)**
- Uncommon
- NOT associated with ESRD
- Most commonly associated with:
  - Primary Hyperthyroidism
  - Malignancy
  - Alcoholic Liver disease
  - Connective Tissue disease
- High Mortality with leading cause of depth= sepsis
Approach to an Atypical Wound:

- Atypical Wound
  - Biopsy
  - Other Pathology
    - Calciphylaxis
      - Non-Uremic
        - Coumadin? yes
          - Malignancy?
            - Hematology/Oncology Consult
          - Hyperparathyroidism?
            - Parathyroidectomy
          - Alcoholic Liver Disease?
            - Alcohol Cessation
        - Coumadin? yes
          - Stop Coumadin
      - Uremic
        - Coumadin?
          - Sodium Thiosulfate Dialysis
            - Phosphate binders Bisphosphonate HBOT Local Wound Care
          - Connective Tissue Disease?
            - Rheumatology Consult

Bisphosphonate Infusion Local Wound Care

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Wound Features of Calciphylaxis

• Both CUA and NUC wounds present with:
  • Intense Pain
  • Cutaneous lesions with palpable firm calcified cutaneous tissue (1)
  • Most commonly found on distal legs as
    • Indurated nodules (2)
    • Ulcerations with central necrotic eschar (3)
  • Can exhibit Livedo Reticularis (LR) (3)
  • If severe pain + LR are seen = high index of suspicion for either CUA or NUC
  • Usually bilateral, symmetric and can extend to muscle
Diagnosing Calciphylaxis as CUA vs NUC

• Clinical suspicion

• Biochemical values:
  - Calcium, Phosphate or Calcium x Phosphate Product CONFIRMS Calciphylaxis

• Histopathology via Biopsy of Lesion:
  - Show Calcification of the intima & media of the small and medium vessels in the dermis and subQ tissues

• Radiographic: X-rays are not beneficial and not recommended

• Most common: white females in 5th decade but can range from 15-82 years old

Lab Tests to Order: Most often +/-abnormal in CUA

- Serum BUN and Creat levels
- Serum calcium, phosphate, alkaline phosphatase, and albumin levels
- Serum parathyroid hormone (PTH) level

Coagulation factors - PT, APTT, antithrombin III, protein C level, protein S level, anticardiolipin level, lupus anticoagulant level, factor V Leiden level, and homocysteine level

- Cryoglobulin and RF measurements
- Hepatitis C antibody level
- Cryofibrinogen level
- Serum amylase and lipase level
- Aluminum level

Measures of inflammation – ESR & CRP value

To Exclude underlying Vasculitis - Antineutrophilic antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA)
HISTOLOGY of Calcyphylaxis:

- Small Dermal and SubQ arteries and arterioles
  - Calcification
  - Microthrombosis
  - Fibrointimal hyperplasia

- Leading to cutaneous ischemia and intense septal panniculitis

- Theoretical sequences: calcification -> thrombosis -> ischemia
RISK FACTORS:

- **Diabetes**
  - Frequent co-morbidity. No data available regarding whether DM control or duration affects calciphylaxis risks

- **Obesity**
  - Risk factor for proximal calciphylaxis (trunk, thighs, breast, etc)

- **Autoimmune Conditions**
  - SLE, RA

- **Infectious, autoimmune, and alcoholic hepatitis**

- **Hypoalbuminemia**

- **Coumadin**
Clinical Presentation

- Skin lesions appeared as
  - indurated nodules
  - necrotic eschars
  - Ulcerations
  - dry gangrene
  - livedo reticularis

- Severe painful lesions with poor healing and frequently complicated by blistering and ulceration with superimposed infections

- Ulcerations commonly are covered with black eschar

- Legs, abdomen, and buttocks in 60%, 23%, and 9% of cases, respectively
Differential Diagnosis for Calciphylaxis

• High index of suspicion of:
  • Pyoderma Gangrenosum
  • Calcinosis Cutis/Atrophie Blanche
  • Coumadin Necrosis (Abdomen)
  • Malignant Melanoma/SCC
  • Venous Stasis/Arterial/Mixed
Morbidity & Mortality

**Morbidity**
- Severe pain
- Non-healing wounds
- Recurrent hospitalization
- Adverse effects of treatment

**Mortality**
- 1-year mortality rate = 45-80%
- Sepsis is the leading cause of death
- Mortality Rate in chronic hemodialysis pt
  - 3x higher in pt with calciphylaxis
Case Study: 75 y.o. White, Female:

- Pt presented with painful, chronic, non-healing wounds on her left lower extremity.
- Currently on Coumadin for atrial fibrillation.
- Denies smoking, drinking alcohol, or illicit drugs use, and NKDA
- Patient had seen several doctors prior to seeing the authors, and failed various conservative treatments, including various topical ointments (Santyl, Silvadene, triple antibiotic, etc), compression wraps, and local wound care.
- Patient did have a biopsy performed prior to seeing us and the pathology report suggested livedoid vasculopathy.
- Wound on left LE had present for 2 years
LLE Wounds

Initial Left Lower Extremity Wounds
Post 1st Compression
LLE wounds healed

Left Leg healed after 8 weeks

Not the end of the Story...
GUESS WHAT WAS HIDING FOR ME ON THE Right Leg ??

B.O.G.O
Right LE initial presentation
Approach to an Atypical Wound:

1. **Atypical Wound**
   - Biopsy
   - Other Pathology

2. **Calciphylaxis**
   - Non-Uremic
     - **Coumadin?**
       - yes: **Stop Coumadin**
       - no: Malignancy?
         - yes: Hematology/Oncology Consult
         - no: Hyperparathyroidism?
           - yes: Parathyroidectomy
           - no: Alcoholic Liver Disease?
             - yes: Alcohol Cessation
             - no: Connective Tissue Disease?
               - yes: Rheumatology Consult
               - no: Sodium Thiosulfate Dialysis Phosphate binders Bisphosphonate HBOT Local Wound Care

3. **Uremic**
   - **Coumadin?**
     - yes: Coumadin
     - no: Other Pathology
Gathering your TOOLS: it takes a village…

- No matter your specialty you need to use all your resources:
  - **Patient & Family**
  - Podiatrist/LE wound specialist
  - PCP/Internist
  - Dermatologist
  - Nephrology
  - Pain Management
  - Nurses (key factor in Dressing changes and compression)
  - Infusion Team
  - Palliative care/Psychology
RLE wounds took a different course

- Patient had discolored spots on the posterior, medial, and lateral of right distal leg.
- Patient was initially treated with Coban™ 2 Lite compression wrap.
- Worsened at follow up visits with increased pain
- The dark spots had transformed into extremely tender reticulate purpura with black eschar and violaceous borders. No drainage or open wound noted.
- Pain on the RLE was 10/10  LLE stabilized.
- Suspected PG on the RLE like LLE
- Started another course of oral steroid treatment (weekly tapers starting at 60mg); unfortunately, there was not any noticeable improvement.
- A 4mm skin punch biopsy → confirmed calciphylaxis.
Show a calcific vasculopathy in the subcutaneous tissue

Ischemic and calcific changes
Consistent with the diagnosis of Calcyphylaxis

Histopathology confirmed Calcyphylaxis:
Patient Workup:

• Vascular consult
  • No vascular disease, and her LLE had minimal reflux and arterial studies were unyielding.

• CBC, CMP, and PTH level WNL

• + DM with A1c <6%, No History of Dialysis, normal kidney function (NEPHROLOGY did not recommend treatment b/c it was NUC)

• Requested that her PCP d/c use of Coumadin convert to Xarelto
  • persistently necrotic with no improvement after discontinuing Coumadin

• Discussed with wound team (MD, DPM, RN and NP)
  • Some outliers: RECOGNIZED THE NEED FOR CONSISTENT COMPRESSION AND APPLICATION
Known Infusion Therapies Options:

**Sodium Thiosulfate Infusion**

Sodium thiosulfate is a potent antioxidant, and it also increases the
*solubility of calcium deposits.* Success has been reported in uremic
and nonuremic calciphylaxis. Often used in combination with HBO,
and combination meds.

**Pamidronate Infusion**

This is a Bisphosphonate: it increases osteoprotegerin production and
inhibits arterial calcification. Works without changing calcium or
phosphate levels.
Treatment Standard for Calciphylaxis CUA

Medical Treatment Options

• Phosphate Binders
• Sodium Thiosulfate
• Bisphosphonates
• Decreased Ca+ in Dialysate
• Antibiotics
• Low Phosphate Diet
• Avoidance of challenging agents
  ❖ Avoidance of systemic steroids
  ❖ Anticoagulation
  ❖ HBO

Surgical Treatment options

• Parathyroidectomy
• Wound care and Debridement
• Amputation
• Renal Transplantation
• Skin Grafting
Treatment Decided on: Pamidronate disodium

- Scheduled for 4 treatments of pamidronate disodium 30mg infusion every two weeks along with local wound care, pain management, wound measurements and weekly compression wrap
- With each infusion, patients right leg wounds continued to improve and eventually closed after 6 months
What does the literature show:

• Bisphosphonate:
  • Pamidronate – drug for hypercalcemia in malignancy, Multiple myeloma, Paget Dz,
    • Used to decreased hypercalcemia
    • In a case report, six doses of IV Pamidronate therapy (30 mg per dose) resolved the CUA lesions in a chronic kidney disease (CKD) patient

• Most studies out there use the kitchen sink method: Thiosodium sulfate, HBO, dialysis, etc

• No general consensus of how to approach NUC.
2 weeks Post 1st infusion Therapy
4 month since initial presentation
Healing after 3\textsuperscript{rd} infusion therapy
Healing post 4th infusion therapy
Status post 5\textsuperscript{th} month
1 month following 4\textsuperscript{th} infusion
Status Post 6th month from start of Infusion Therapy
Conclusion

• NUC can be easily misdiagnosed as other types of wounds

• Future Study
  • Large cohort of NUC patient treated solely with pamidronate and local wound care

• Could this be the next treatment guideline for NUC?

• Why consider a single drug therapy option:
  • Reduce drug-drug interaction
  • Increase compliance in patient
  • Reduce cost
  • Reduce side effects
Atypical Wound

Biopsy

Other Pathology

Calciphylaxis

Non-Uremic

Coumadin?

yes

Stop Coumadin

Uremic

Coumadin?

yes

Coumadin?

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Thank you!

Enjoy the journey!

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