CALCIPHYLAXIS: IS PD A RISK FACTOR?

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OBJECTIVES

• Definition/terminology
• Risk Factors/Pathophysiology
• PD as a risk factor: The Evidence
• Management

“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 is characterized by 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*


CUA: HISTOPATHOLOGY


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
- Erythropoetin


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

PD AS A RISK FACTOR: THE EVIDENCE
Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy

Adrian Fine and James Zacharias

- 36 patients with diagnosis of CUA over 7 years
- Incidence of 4.5/100 patient-years
- 28/36 (78%) on PD
- 80% with non-ulcerating lesions
- Bone scan positive in 97% of patients
- PD, Female sex, Diabetes – risk factors
- Case-control study: phos level, Ca X P, being on Ca salts + Vit D predicted disease

- 59 patients with CUA between 1998-2006,
- 54 were on PD
- In the PD population, the mean yearly incidence from 1998 to 2003 was 4.5/100 patient-years, falling to 1.3/100 patient-years in 2004 – 2006
- The percent of patients not taking calcium salts fell during this time period
- Marked discrepancy noted between ionized and corrected serum calcium thereby missing hypercalcemia
- Marked improvement on switching to HD
DISCREPANCY BETWEEN IONIZED AND TOTAL CALCIUM

New et al., Int J of Nephrology, 2011

Figure 2 — Comparisons between ionized and corrected serum calcium levels in our dialysis population (both hemodialysis and peritoneal dialysis). Both measurements were made on the same samples.
PD AS A RISK FACTOR

- Increased incidence in PD population described previously
- Reasons unclear; but one study suggested link to high calcium supplementation
- Patient characteristics similar to those of HD
- Association needs to be studied further
- Management similar except for the possibility of intraperitoneal STS

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

*Giachelli CM. JASN 15: 2004

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, ?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

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

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. Adv chr kid dis, 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, neoangiogenesis, 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

Girotto JA et al., Surgery 2001

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

INTRAPERITONEAL STS

• Possible, but risk of chemical peritonitis

• Not used in our practice
INTRALESIONAL STS

Intralesional STS 250 mg/ml diluted 1:1 with 1% lidocaine—led to complete healing of lesions in 4 patients

Localized discomfort during injection

OTHER OPTIONS

• Corticosteroids
• Bisphosphonates
• Tissue Plasminogen Activator

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
- PD has been described as a risk factor in previous studies, but has not been substantiated recently
- Reason for higher incidence in PD unclear; could be due to high use of calcium salts
- Multidisciplinary approach is key in the management of CUA
- STS in addition to aggressive wound management, calcium-phosphorus control
- Evolving role of Vitamin K supplementation
- High mortality despite treatment

Thank You!