Calciphylaxis:

Pain management in renal impairment

Anica Vasic
Pain Management Unit
St George Hospital
Sydney

- 1961 Hans Seyle coined term “calciphylaxis” to describe a condition of induced hypersensitivity in which tissues respond to appropriate challenging agents with tissue calcification.
- Step 1: sensitization by agents such as parathyroid extract, high dose vitamin D, high phosphorous diet or induction renal failure
- Step 2: challenging agent such as local trauma
- Result: Subcutaneous calcification (calci-) as an adaptive or protective reaction (phylaxis)

Selye H. The dermatologic implications of stress and calciphylaxis. J Invest Dermatol. 1962;39:259–275.

Experimental Calciphylaxis	Human Calciphylaxis
No small artery/arteriolar calcifications	Calcification, microthrombosis, fibrointimal hyperplasia of small dermal and subcutaneous arteries/arterioles
Animals able to cast off calcified skin molt and replace with new dermis with no features of calciphylaxis	Skin manifestations predominate but can also have vascular calcifications in skeletal muscle, brain, lungs, mesentery
Able to be prevented by administration glucocorticosteroids	No response to steroids

- Also known as calcific uraemic arteriolopathy
- Rare
- 1-4% dialysis patients
- Can also occur in nonuraemic, non dialysis patients
- Female 2:1
- Obesity (BMI>30) lesions occur on trunk, thighs, breasts
- Diabetes: no data whether control or duration changes risks

Co-Morbid Conditions

- Auto immune conditions such as SLE, Temporal arteritis, rheumatoid arthritis
- Drugs used in the management of above such as corticosteroids, methotrexate, ultra violet light
- Hypercoagulable conditions such as protein C and protein S deficiencies
- Longer dialysis vintage > 7 years
- Hypoalbuminaemia

Medications increasing risk

- Calcium supplements
- Calcium based phosphate binders
- Warfarin
- Corticosteroids
- Iron therapy
- Trauma associated with subcutaneous insulin/heparin injections

- Mortality high, within months of diagnosis
- One year mortality 45-80% in those with ulcerated lesions
- Lower extremity involvement associated with lower mortality (23%) compared trunk and proximal limbs (63%)
- Morbidity related to severe pain, non healing wounds, recurrent hospitalisations
- Death usually secondary to sepsis

Failu Alison Rich, A Leach, J Ellershaw, Difficult Pain in Chronic Renal re and Calciphylaxis. *JPain Symptom Management* 2001, 22:617-621

Weenig RH, Sewell LD, Davis MD, McCarthy JT Calciphylaxis: natural history, risk factor analysis, and outcome. Journal of the American Academy of Dermatology 2007; 56(4):569-579

Pathogenesis

- Poorly understood
- Hyperparathyroidism may be implicated but not consistent.
- Ca x PO_4 product **may** be important
- Vitamin D administration in high doses may induce calciphylaxis ?increasing serum phosphate ?direct action on arterioles

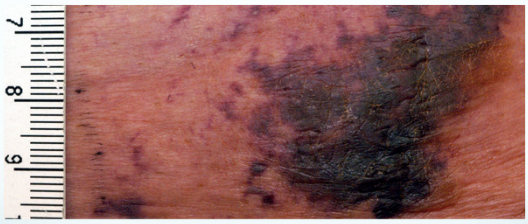
What do we see?

mottled skin (livedo reticularis)

Nodules

Purpuric plaques

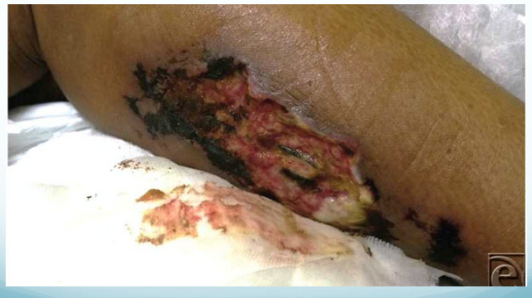
Necrosis skin, subcutaneous fat, muscle



Niels Olsen 2009

Lesion on abdominal wall

Erythema, ecchymosis, necrosis



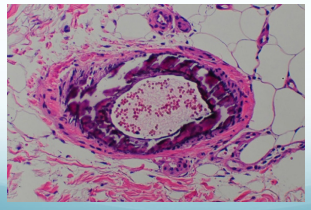
www.medscape.com

Histological features

- Calcification of medial wall of arterioles
- Intimal proliferation and fibrosis, endovascular thrombosis
- Ischaemic pathology distal to vessels

Diagnosis

- Skin biopsy BUT risk of ulceration, infection, bleeding, induction necrosis, propagation new lesions
- Punch biopsy (4-5mm deep) recommended



Treatment

- Treat calcification
- Treat ulcers
- Treat pain
- SUPPORTIVE

Sodium thiosulphate

- Thought to dissolve calcium deposits by forming soluble complexes
- May act as antioxidant to restore endothelial function and promote vasodilatation ➔improving pain
- 30-60 mins towards end dialysis
- 25mg (in 100mls saline) x3 week

Adverse N&V headache hallucinations

Bisphosphonates

- Action inhibits macrophages and proinflammatory cytokines
- Binds to calcified smooth muscle to inhibit further calcification
- Removed by haemodialysis
- Pamidronate 30mg iv x 5 doses
- Adverse: fever, pain at injection site

Hyperbaric Oxygen Therapy

- 25-30 sessions at 2.5 atmospheres
- To promote healing of ulcers
- Limited number of studies

Opioids in Renal Failure and Haemodialysis

- Parent drug
- Metabolites

} Renal Failure

- Parent drug
- Metabolites

} Dialysis

- GFR approximates excretion of many drugs

Dialysis

- Role of clearance of a drug and its metabolites is complex
- Removal in dialysis depends on molecular weight, water solubility and volume of distribution: protein binding
- Dialysis process itself may vary e.g. pore filter (area, pore size, geometry of filter technique) flow rate of patients blood and of dialysate fluid.
- Peritoneal v haemodialysis

Morphine

- Metabolised by liver
- Morphine-3-glucuronide (55%), Morphine-6-glucuronide (10%), normorphine (4%)
- parent compound excreted normally in renal failure
- ↑M-6-G in renal failure (as glucuronide excretion is affected)
- Crosses BBB slowly, CNS effects can be prolonged after discontinuation morphine
- Dialysis: Low protein binding, moderate water solubility → removed by most procedures **BUT** glucuronides would accumulate

Hydromorphone

- Metabolized in liver: hydromorphone-3-glucuronide(36.8%),dihydromorphone (0.1%) and other lesser metabolites
- H-3-G neuroexcitatory and accumulates in renal failure but not clear whether clinically effect
- No change in dosage recommended
- Dialysis: low volume distribution, high water solubility, low protein binding→dialyzable
- Use carefully and monitor patient

Oxycodone

- Excreted as conjugated and free oxycodone (8-14%)
- Oxymorphone only active metabolite, low plasma levels
- Excretion slowed in renal failure but little known of effect
- Dialysis: water soluble, 50% protein bound →dialyzable no definitive data
- Best to avoid in dialysis

Methadone

- Metabolised to a pyrrolidine then to pyrroline both hydroxylated
- Excreted in urine (20-50%) as methadone or metabolites
- Excreted in faeces (10-45%) as pyrrolidine metabolite
- No changes in excretion in renal failure
- Dialysis: high protein binding and high volume distribution, moderate water solubility→ poorly removed
- No accumulation→ safe to use (usual precautions)

Codeine

- Metabolised to codeine-6-glucuronide (81%),morphine, morphine3G (2%) and morphine6G(<1%)
- Significant decrease in clearance in renal failure
- Accumulation of metabolites
- Significant accumulation in haemodialysis with toxic effects
- Do not use

Gabapentin

- Renal excretion as unchanged drug
- Clearance reduced in renal impairment and half life increased
- Suggested reduced dosage (at same intervals)
- 3% protein bound, moderate volume of distribution
- Dialysis: recommended supplemental dose after dialysis in addition to usual dosage

Pregabalin

- Negligible metabolism
- Renal excretion as parent drug
- Dialysis: not bound to plasma proteins, 50% reduction plasma levels after dialysis
- supplemental dose following 4 hour haemodialysis

Case#1

RI 72 year old male

ESRF diabetic nephropathy on dialysis

Type 11 diabetic on insulin

Ischaemic heart disease

Hypertension

Pulmonary hypertension

Atrial fibrillation

Obesity 114kg

- Bilateral lower limb lesions
- Background neuropathic pain
- Pain++ on dialysis
- Amitryptiline 50mg
- Gabapentin 300mg tds
- Paracetamol 1G tds
- Hydromorphone 1mg q2hrly usually on dialysis
- Sodium thiosulphate 25gm ivi 60 mins post dialysis

- Continuing pain
- Worsening ulceration lesions lower limbs
- Hyperbarric oxygen considered
- Contraindicated due to pulmonary hypertension
- Increased analgesic requirements on dialysis
  - ?removal by dialysis of opiates
  - ?ionisation changes

- PCA fentanyl 10µ increased to 20µ
- Ketamine 8mg/hour s/c
- Hydromorphone oral (Jurnista)
- ↑ right leg pain
- ulceration worsens

- Decision to perform right below knee amputation
- Gabapentin increased
- Ketamine infusion peri-op
- Femoral sheath with local anaesthetic
- Hydromorphone regular with breakthrough
- Left leg amputated 3 weeks later

- 4 years later still on dialysis
- phantom limb pain controlled with gabapentin

Case#2

- MT 57 male
- ESRF diabetic nephropathy
- Hypertension
- Ischaemic heart disease
- Implantable defibrillator
- Accidentally knocked right calf

- Developed skin lesion
- Not noticed for three weeks
- Necrotic, infected ulcerating lesions
- Commenced hydromorphone q2hourly
- Gabapentin 100mg after dialysis
- Ketamine infusion 10mg/hour
- Sodium thiosulphate 25mg after dialysis

- Septic given antibiotics
- Increasing pain
- Increased doses gabapentin, now regular 300mg bd
- Jurnista increasing doses to 48mg/day
- Breakthrough hydromorphone
- Still in pain

Failu1 Alison Rich, A Leach, J Ellershaw, Difficult Pain in Chronic Renal re and Calciphylaxis. *JPain Symptom Management* 2001, 22:617-621

2 Mervyn Dean, Opioids in renal failure and dialysis patients *JPain Symptom Management* 2004, 28:497-504

3 Peter Santos, J Edward Hartle and L Darryl Quarles, Calciphylaxis *2013UpToDate*

4 Peter Monney et al, Rapid improvement of calciphylaxis after intravenous pamidronate therapy in a patient with chronic renal failure *Nephrol. Dial.Transplant. (2004) 19 (8) 2130-2132*

5 Natasha Rogers et al, Hyperbaric oxygen as effective adjuvant therapy in treatment of distal calcific uraemic arteriolopathy *NDT Plus (2008) 1 (4) 244-249*

Peripheral Vascular Disease

Pain Management in ESKD

- Chronic kidney disease (CKD) is independent risk factor for generalised atherosclerosis and coronary artery disease
- Lower limb peripheral artery disease significant clinical issue in patients with CKD
- Increased number of studies now describe association between PAD and CKD

Older age is associated with higher prevalence of known risks such as cardiovascular disease, diabetes, hypertension

After adjustment for these possible confounders:

CKD is independently associated with increased prevalence of PAD

Symptomatic PAD

- More prevalent in those with CKD than general population
- Intermittent claudication
  - in general population 1-5%
  - In CKD 7% (as high as 12% Some studies)
- Incidence of lower limb “incident” rates (eg need for revascularization, amputation)
  - In CKD 2.7%
  - N renal Function 0.6%

Clinical

- Similar to patients without CKD but
  - More likely to develop critical limb ischaemia
  - Have higher rates of limb loss after revascularisation
  - Higher mortality

How do we diagnose?

- Ankle-Brachial Index (ABI)
  - Measure systolic both arms
  - Measure systolic at ankle of affected limb
  - Ratio <0.90 indicates PAD
  - BUT
  - In CKD higher rates of vessel calcification leading to abnormal low pressure due to arterial incompressibility
  - >1.3 indicates calcification

- Vascular duplex studies
- Exercise ABI (after treadmill stress)
- CT angiography
- MRAngiography
- Angiography

- Usually reserved if contemplating revascularisation
- (risk dye)

Treatment PAD?

- Few studies have evaluated impact of medical treatment on peripheral artery disease outcomes

- Recommendations for treatment are extrapolated from described or presumed benefit of interventions in reducing cardiovascular events or modifying markers of cardiovascular risks

Risk Factor Modification

- Statin therapy to reduce overall frequency of cardiovascular events
- Antihypertensives to reduce risk cardiovascular events, delay progression of CKD
- Smoking cessation-although not studied in this population smoking is associated with increased risk amputation among patients with claudication

- Anti platelet therapy – aspirin or clopidogrel
- Reduce risk cardiovascular events
- May improve patency rates after revascularization

- Cilostazol- phosphodiesterase inhibitor has both antiplatelet and vasodilator properties
  - Increases pain free and claudication distance
  - Contraindicated in heart failure

- Exercise- first line therapy for intermittent claudication

Invasive treatment

- Indications no different to general population
- More likely to undergo amputation
- Higher mortality and lower limb salvage rates
- Revascularisation has lower mortality rates than amputation or no interevention

- Society for Vascular Surgery Lower Extremity Guidelines Writing Group J Vasc Surg2015; 61:2S-41S
- National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease: Stratification of Risk for Progression of Kidney Disease and Development of Cardiovascular Disease (2002)
- Garimella, Pranav S. Hart, Peter et al: Peripheral Artery Disease and CKD Am J Kidney Dis. 2012;60 (4):641-654

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