CALCIFIC UREMIC ARTERIOLOPATHY

10.28.14

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Renal Fellow
CASE

• 45 Hispanic Female

• Chief Complaints:
  • Confusion x 1 day
  • Fatigue, sore throat, painful oral ulcerations x 1 week
  • Increased bilateral LE swelling x 1-2 weeks
  • Worsening emesis, poor appetite, lethargy x 2 weeks
CASE: HPI

- Well known to renal clinic since 2011, h/o CKD due to diabetic nephropathy (with diabetic retinopathy) and a question of PKD

- Last seen in clinic in March 2014

- AVF created in April 2014, patient had gone to Mexico after that

- Symptoms started in Mexico, present for about a month
CASE: PMH/PSH

- CKD Stage 5
- DM2 X 12 years
- HTN
- PKD
- Hypothyroidism
- Morbid Obesity
- AVF creation April 2014
- Cholecystectomy, tubal ligation
MEDICATIONS

- Amlodipine 10 mg po d
- Synthroid 125 mcg po d
- HCTZ 25 mg po d
- Lantus 10 units bid sc
- ASA 81 mg po d
HISTORY

• Family: Father and 2 daughters with PKD, no one with ESRD

• Social: no toxic habits
PHYSICAL EXAM

• **Vitals:** T 96.3, 83, 18, 134/53, 100% RA

• **Gen:** Somnolent, arousable and responding to commands

• **HEENT:** tongue coated with whitish, shallow ulcerations lateral edges of tongue, bleeding +

• **CVS:** S1S2+, RRR, 3/6 SM LUSB/LLSB, no rubs

• **Resp:** Transmitted upper airway sounds, otherwise clear

• **Abd:** Obese, soft, non tender, non distended, +BS

• **Ext:** varicosities, edema 1+ to b/l shins, tenderness over LE (legs and thighs bilateral, subcut nodules), L AVF palpable thrill and bruit
Labs

**LFTs:**
- ALT: 26
- AST: 17
- AlkP: 164
- Tbili: 0.1
- Dbili: < 0.1
- TP: 6.6
- Alb: 3.1

**Rapid Strep Test:** Negative

**Urine Studies:**
- UA: Bld 3+, pH: 7.5,
  - Protein: > 300 mg / dL,
  - WBC: Packed, RBC: 5 – 10,
  - Bacteria: Many

- Urine Prot / Cr: 2 g / g

**Biochemistry:**
- Phos: 13.6
- iPTH: 315.4
- Vit D: 15
- Ca: 6.3
- Glu: 109
- Protein: > 300 mg / dL
- WBC: Packed
- RBC: 5 – 10
- Bacteria: Many

**Urine Prot / Cr:** 2 g / g
• US Abdomen
  • RK 16.2, LK 13.3 cm
  • Increased echogenicity compatible with intrinsic renal disease
  • Both kidneys with multiple, numerous cysts, largest on RK upper pole 3x2.7x3.1, LK mid to lower pole 2.5x2.3x2.5 cm
  • No hydronephrosis

• CXR: clear lungs
HOSPITAL COURSE

• Patient was started on Hemodialysis

• Developed progressive pain over LE with violaceous tender plaques which later ulcerated
Day 7
DIFFERENTIAL DIAGNOSIS

- Calciphylaxis
- Cellulitis
- Panniculitis
- Erythema Nodosum
- Cryoglobulinemia
ADDITIONAL LABS

- HIV neg
- ANA, RF, Hep B, C panel, APLA panel, Cryo: negative
- dsDNA, anti Smith, anti RNP: all negative
HOSPITAL COURSE

• Biopsy taken of a lesion over R medial thigh

• LLE X-ray
R Medial thigh lesion biopsy
R Medial thigh lesion biopsy
• Started on Sodium thiosulfate
• D/C Ca containing binders, vitamin D
• Frequent HD
• Sevelamer, Cincalcet
• Local wound care with Silver sulfadiazine
• Pain control
HOSPITAL COURSE

• Progressively worsening ulcers

• Development of similar lesions over lower abdomen
FURTHER HOSPITAL COURSE

• Also complicated by septicemia and AMS

• Blood cultures with Coagulase negative staph

• Started on antibiotics

• AMS improved after 2 days

• Progression of ulcers
CALCIFIC UREMIC ARTERIOLOPATHY
• Rare disorder with mortality around 80%

• 1962: Hans Selye coined “Calciphylaxis” to describe skin necrosis in rats exposed to PTH, Vit D and associated cutaneous calcification

• Histopathology different from syndrome described in uremic patients, no vascular calcifications

• Coates suggested the term Calcific Uremic Arteriolopathy

P. Yerram at al. The Ochsner Journal 14: 2014
Branderburg et al Ped Nephrol Jan 2014
EPIDEMIOLOGY

• Exact prevalence unknown

• Small studies report 4% prevalence in HD patients and 1.3-4.5 per patient years in ESRD

• Several registries: Germany, UK, Kansas University Med Center

P. Yerram at al. The Ochsner Journal 14: 2014
Registries
• Previously thought to be a passive process described under “Metastatic Calcification”

• Vascular calcification now known to result from active cellular processes and not just passive mineral precipitation

• Cutaneous arterial calcification and vascular thrombosis both required to produce clinical lesions

Jablonski et al Hemodialysis Int Oct 2013
Cuo-Cheng et al Scientific World Journal July 2014*
PATHOPHYSIOLOGY

Active Process
Transformation of VSMCs to Osteogenic/Chondrogenic Phenotype

Passive Process
Mineral precipitation of ECF surrounding VSMCs

- Jablonski et al. Hemodialysis Int Oct 2013
<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Caucasian race</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Chronic kidney disease/end stage renal disease</td>
</tr>
<tr>
<td>Low serum albumin</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
</tr>
<tr>
<td>Calcium-based phosphate binders</td>
</tr>
<tr>
<td>Calcium-phosphate product $&gt;70 \text{ mg}^2/\text{dL}^2$</td>
</tr>
<tr>
<td>Time on dialysis</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
</tr>
<tr>
<td>Protein C and/or S deficiency</td>
</tr>
<tr>
<td>Use of warfarin, corticosteroids, iron dextran, erythropoietin</td>
</tr>
</tbody>
</table>
Vascular Calcification Promoters

Vascular Calcification Inhibitors

- Jablonski et al Hemodialysis Int Oct 2013
- Schroppet KI 2008
PATHOPHYSIOLOGY

Promoters
- Ca/P04 homeostasis dysregulation in CKD
- FGF23/Klotho
- BMP2/RANK/RANKL
- Inflammation/ROS

Inhibitors
- MGP
- Fetuin A
- Pyrophosphate
- OPG
- BMP 7

Adapted from Kuo-Cheng et al Scientific World Journal July 2014
Uremic Environment

- Uremic toxins
- Oxidative stress
- Inflammation
- TNFα
- Wnt pathway
- Elevated Ca
- MMP2/9
- Elastin degrade
- TGFβ
- Induce phosphatidyl serine and annexins
- OH-apatite nucleation complexes on VSMC memb surface
- Elevated Po4
  - Stipulate EC to form μparticles
  - Activate Wnt/B catenin pathway
  - Up reg mRNA exp for osteogenic factors via Pit1 and 2
  - Apoptosis

Adapted From
Shanahan, C. Nat Review Nephrol Sept 2013
Kuo-Chen et al. Scientific World Journal July 2014
Tomasz S. World J Cardiol 2014 April 26
Paloian et al AJ Renal Phy Aug 2014
FGF 23 AND KLOTHO

FGF 23 (Phosphatonin):
- Synthesized by osteocytes
- Regulator of Po4 and Vit D metabolism
- FGFR expressed ubiquitously

Klotho:
- Expressed mainly in PTH gland and Kidneys
- Coreceptor for FGF 23

Olauson et al Curr Opin Nephrol HTN 2013
Jimbo et al KI 2013
Tomasz S. World J Cardiol 2014 April 26
FGF23

- NaPi-2a
- NaPi-2c

↓ Phosphate excretion

↓ Serum phosphate level

↓ 1-α hydroxylase
↓ Calcitriol

↓ Phosphate absorption
MARKER OF VASCULAR CALCIFICATION IN CKD

• FGF23 early marker in CKD

• In response to phosphate, klotho decline, pathomechanistic relation to CKD progression

• Epidemiological studies reported association between high EGF 23 and poor outcome in CKD

• Klotho Independent studies:
  • Landmark study by Faul et al, LVH in mice
  • Phos induced vascular calcification in aortic rings from uremic rats (Jimbo et al, KI 2014)

PROPOSED MODEL FGF 23 AND KLOTHO DYSREGULATION IN CKD
INHIBITORS

MGP

- Binds Ca: inhibits supersaturation and crystallization within vessel walls
- Binds OH apatite crystals, inhibit growth
- Inactivates BMP 2
- Needs Vit K for carboxylation

Pyrophosphate

- Blocks hydroxyapatite nucleation and crystal growth
- Prevents further phosphate attachment
- Degraded by ALP

Fetuin A

- Calciprotein particles
- Loaded into matrix vesicles of synthetic VSMCs

Adapted From
Shanahan, C. Nat Review Nephrol Sept 2013
Danziger, J. CJASN 2008
Elevated P

MGP
Fetuin A
Pyrophosphate

Contractile VSMCs (regulate tone)

Runx2

Synthetic VSMCs (adaptation/repair)

Elevated P
Elevated Ca

Loss of endogenous inhibitors

Increased osteogenesis (Alkaline phosphatase)

Osteochondrocytic VSMCs (mal-adaptation/calcification)

Apoptosis
Necrosis

Nanocrystals deposited

Endocytosis of nanocrystals
CLINICAL FEATURES

• Painful nodules or violaceous mottling

• Acral lesions and proximal

• Progress and expand, hemorrhagic, ulcerate, eschars form

Llach KI 2003
J AM Dermatol 2008
Yerram The Oschner J 2014
DIAGNOSIS

- Clinical picture
- Skin biopsy
- Bone scintigraphy
TREATMENT
Sodium Thiosulfate Therapy for Calcific Uremic Arteriopatohy

Sagar U. Nigwekar, Steven M. Brunelli, Debra Meade, Weiling Wang, Jeffrey Hymes, and Eduardo Lacson Jr.
MECHANISM OF ACTION

• Exact mechanism elusive

• Calcium chelation hypothesis challenged

• Direct extracellular effects of inhibiting calcification independent of Ca binding

• Antioxidant and vasodilatory mechanisms
MATERIALS AND METHODS

• Systematic observational study: 172 patients undergoing maintenance HD at FMCNA between Aug 2006-Jun 2009

• Study data obtained from FMCNA clinical information system

• Lab related and weight related data collected 90 days before, during and 90 days after STS

• 2 part questionnaire for survey
• Study outcome of CUA: Based on survey responses and mortality data

• Safety outcomes
RESULTS

• 172 patients: 147 completed STS therapy, 53 were “surveyed”

• Baseline Characteristics: Avg age 55 yrs, 74% females, 56% white

• CUA confirmed with skin biopsy in 47% of surveyed patients, legs (60%), abd (23%), buttocks (9%)
RESULTS

• STS Therapy: 43 pts out of 53 surveyed completed

• Outcome of Survey:
  • 26.4% < complete resolution > 30.2%
  • 18.9% < marked improvement > 18.6%
  • 28.3% < improved > 18.6%
  • 5.7% < did not improve > 7%
  • 20% < unknown > 25.6%

• Mortality: Overall 42%, 1 yr in treated patients 35%

• Safety:
  • 19% nausea, 15% vomiting. Bad taste, periorbital tingling
  fatigue rare
  • Na, AG higher; Phos, Bicarbonate, post dialysis weight
  lower compared to pre treatment levels
SURVEYED VS NON SURVEYED PATIENTS

Figure 3. Kaplan-Meier survival curves comparing surveyed and nonsurveyed patients treated with sodium thiosulfate.
CONCLUSIONS

• STS reasonably safe during Rx of CUA in maintenance HD patients

• Majority demonstrated clinical improvement
LIMITATIONS

• No control group

• Histological diagnosis available in less than half

• Selection bias, potential exclusion of hospitalized patient

• No data on concurrent risk factors (warfarin)
Multi-Modal Treatment Of Calciphylaxis With Sodium-Thiosulfate, Cinacalcet And Sevelamer Including Long-Term Data

Hermann Salmhoferab, Michael Franzenab, Wolfgang Hitzlc, Josef Koller d
Bernhard Kreymannb, Falko Fendf, Cornelia Hauser-Kronbergerf
Uwe Heemannb, Frieder Berr a, Christoph Schmadererab

Case Report/Case Series

Intralesional Sodium Thiosulfate for the Treatment of Calciphylaxis

Lauren Strazzula, BA; Sagar U. Nigwekar, MD; David Steele, MD; William Tsiaras, MD, PhD; Meghan Sise, MD; Sabina Bis, MD; Gideon P. Smith, MD, PhD; Daniela Kroshinsky, MD, MPH
LDL-apheresis dramatically improves generalized calciphylaxis in a patient undergoing hemodialysis

Masao Iwagami, Yasuhiro Mochida, Kunihiro Ishioka, Mochida Oka, Hidekazu Moriya, Takayasu Ohtake, Sumi Hidaka, and Shuzo Kobayashi

Department of Nephrology, Immunology, and Vascular Medicine, Shonan Kamakura General Hospital, Kanagawa, Japan
Published in final edited form as:


**Pilot Study of the Effect of Lanthanum Carbonate (Fosrenol®) In Patients with Calciphylaxis: A Wisconsin Network for Health Research (WiNHR) Study**

Micah R Chan¹,*, Fadi Ghandour², Narayana S. Murali³, MJ Washburn⁴, and Brad C. Astor¹,⁵
OTHER THERAPIES

• Supportive: Aggressive wound care

• Decrease high CaxP: HD, discontinue calcium products, Vit D, Calcimimetics

• Avoid VKAs
VIT K VS VIT K ANTAGONISTS

KM McCabe et al. KI 2013
Schurgers editorial KI
Progressive renal failure

\[ \downarrow \text{FGF23} \]
\[ \downarrow \text{PO}_4 \text{excretion} \]

Dysregulated bone metabolism

Mineral release
- OPG
- PTH
- Klotho
- FGF23

Common mineralization regulators
Death/“damage” signals

Vascular calcification

Local inhibitors in VSMC vesicles
- Fetuin-A
- MGP

Circulating inhibitors
- Fetuin-A
- PP
- Others?
- Matrix vesicles?
- Hydroxyapatite?

VSMC damage

Matrix vesicles and apoptotic bodies

Loss of inhibitors
- MGP
- Fetuin
- Klotho
- OPG?

Osteo/chondrocytic transdifferentiation

Mineral nucleation in matrix vesicles

Mineral deposition