RENAL MANIFESTATIONS OF SCLERODERMA

SONIKA PURI
SCLERODERMA

- Chronic multisystem disorder with annual incidence of 1-2/100,000

- Peak age of onset is 30-50yrs, F >> M

- TWO SUBSETS:
  Limited Cutaneous SS (Lcss)- hands/face/feet and forearm
  Diffuse cutaneous SS (Dcss)-extensive skin involvement including above elbows and knees and involving the trunk.

-a/w PAH and renal failure; upto SSc patients with PAH have eGFR < 60ml/min
REPORTED RENAL MANIFESTATIONS:

- Scleroderma renal crisis
- Normotensive Scleroderma renal crisis
- Myeloperoxidase –ANCA associated GN and vasculitis
- Penicillamine associated renal disease
- Anti-phospholipid associated nephropathy
- Microalbuminuria and proteinuria

*Renal Manifestations in scleroderma, Shanmugam- International Journal of Rheum, 2010*
Anca associated GN

- More common in pts with LcSS

- Subacute presentation with progressive renal failure, mild hypertension and proteinuria.

- Postulated that scleroderma vasculopathy exacerbates interaction of ANCA with endothelium near vascular pole with neutrophil activation in glomerulus.

- Steroid responsive, min. response to ACE-I

- Biopsy is often required to exclude scleroderma renal crisis

*Renal Manifestations in scleroderma, Shanmugam- International Journal of Rheum, 2010*
Penicillamine induced RF

- Rarely used now however historically used in treatment of Wilsons, cystinuria, RA, PBC
- 20% of pts develop membranous nephropathy with proteinuria.
- Resolve with cessation of drug.
- Severe cases would require plasmapharesis, steroids and immunosuppression.

*Renal Manifestations in scleroderma, Shanmugam- International Journal of Rheum, 2010*
Anti-phospholipid antibody mediated nephropathy

- Frequency of Apla in scleroderma is no greater than that seen in general population.

- 56% of SSc pts were positive for aPL antibody based on single antibody measurement of anticardiolipin (ACL) or Beta-2-glycoprotein ab of IgM/IgG.

- IgG ACL was a/w elevated s.cystatin C

- a/w development of SRC (21% of patient with apl +/none if neg levels)

Wielosz et al. –Clinical Rheumatolgy 2009
lipid peroxidation: Arachidonic acid/LDL in cell membrane

↓

(free-radical process)

↓

8-epi prostaglandin-

F2alpha (vasoconstrictor)

↓

↑ production of endothelin-1

(elevated levels of PGF2α and ET-1 found in patients with SSc esp with PAH)
ABNORMALITIES IN RENAL PHYSIOLOGY IN SS: Clements et al,

Arthritis and Rheumatism, 1994

- n= 57pts with SSc.
- Mean duration of SSc 8.2yrs (6mths to 31yrs); 31/57 had dcSSc

-Renal plasma flow (para-amino hippuric acid clearance)
-Plasma renin/aldosterone and catecholamine levels

Rest  Response to Cold  Upright  In response to salt depletion
• 8 subjects were tested before and after cold stimulation-supine/sitting.

• Sitting: PRA levels increased by 51+/- 41% (601+/714ng/dl/3hrs)

• In comparison 5 normal women (age 35-39 yrs), pra in response to cold in sitting positon 60 +/-115ng/dl/3hrs (11+/22%)
• PAH clearance was studied in 18 subjects in supine postion/ 18 in sitting position.
• 69% patients had abnormally low PAH values in supine position;
• Value obtained in sitting position was lower than supine position

• No change in PAH clearance after cold stimulation.
Abnormally high PRA levels in 49% of 51 supine patients and 44% of 50 sitting subjects.

After cold stimulation, PRA rose 45+/- 50%.

High baseline PRA levels did not predict onset of SRC.

<table>
<thead>
<tr>
<th></th>
<th>PRA activity (mean +/- Sd ng/dl/3hr)</th>
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<tbody>
<tr>
<td></td>
<td>Supine (n=8)</td>
</tr>
<tr>
<td>Before cold stimulation</td>
<td>1515 +/- 1,284</td>
</tr>
<tr>
<td>During cold stimulation</td>
<td>1391 +/- 912</td>
</tr>
<tr>
<td>% change during cold stimulation</td>
<td>- 2 +/- 28</td>
</tr>
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P <0.0005 vs before cold stimulation, sitting position

P<0.05 vs supine position during cold stimulation.
- Acute sodium depletion using 1mg/kg lasix
- Abnormally high elevation of PRA in patients after lasix was noted in 69% of 39 supine patients and 54% of 28 sitting patients

Figure 3. Unstimulated supine plasma renin activity (PRA) in 51 patients with systemic sclerosis (SSc), including 8 SSc patients who were receiving nonsteroidal anti-inflammatory drugs (NSAIDs) until 24 hours prior to PRA testing. Abnormally high PRA values were noted in 49%. 
Renal vascular damage in SS pts without clinical evidence of nephropathy

- 25 normal volunteer and 25 SSc patients, mean diseases duration of 8 yrs
- None had evidence of renal damage
- Doppler usg for evaluation of RI in main renal artery, interlobar artery, cortical artery

Table 2. Characteristics of the systemic sclerosis (SSc) group and the control group

<table>
<thead>
<tr>
<th></th>
<th>SSc patients (n = 25)</th>
<th>Controls (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.2 ± 9.3</td>
<td>51.9 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>No. male/no. female</td>
<td>2/23</td>
<td>2/23</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>56.7 ± 7.2</td>
<td>67.2 ± 6.1</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.65 ± 0.16</td>
<td>1.76 ± 0.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>92.5 ± 8.7</td>
<td>90.2 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma creatinine, μmoles/liter</td>
<td>96.8 ± 13.2</td>
<td>101.3 ± 12.5</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance/1.73 m²</td>
<td>80 ± 16</td>
<td>87 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>body surface area, ml/minute</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Except for no. male/no. female, values are the mean ± 1SD. NS = not significant.

Arthritis and Rheumatism, Rivolta et al, 1996
Figure 3. Relationship between resistance index values (×100), measured on cortical vessels, and disease duration in patients with systemic sclerosis.

Figure 2. Variations in resistance index values (×100) from the main renal artery to the interlobar artery to the cortical vessels in 25 systemic sclerosis patients (closed circles) and 25 normal controls (open circles) with normal renal function. Values are the mean ± 1SEM. * = p < 0.01 versus main renal artery and versus interlobar artery; ** = p < 0.01 versus main renal artery.
Autoantibodies to ACE-2 in pt’s with CTD, Takahashi et al

• 28 healthy volunteers, 18 pts with CTD with vasculopathy (pah/persistent digital ischemia); 24 pts with CTD w/o vasculopathy
Table 1: Patient demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vasculopathy patients</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18 (17 females, 1 male)</td>
<td>24 (21 females, 3 males)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.5 ± 14.3</td>
<td>46.8 ± 17.8</td>
</tr>
<tr>
<td>Disease entities</td>
<td>SLE (4), SSC (6), MCTD (8)</td>
<td>SLE (21), SSC (2), MCTD (1)</td>
</tr>
<tr>
<td>Constrictive vasculopathies</td>
<td>PAH (5); all patients had SSC; persistent digital ischemia (16)</td>
<td>None</td>
</tr>
</tbody>
</table>

Data presented as n or mean ± standard deviation. PAH, pulmonary arterial hypertension; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; SSC, systemic sclerosis.

Figure 2 Inhibition of angiotensin-converting enzyme 2 activity by IgG purified from patient serum. (A) Purified IgG from the sera of healthy volunteers (H1 to H3) and patients with vasculopathy (P1, P5, and P6) was detected by SDS-PAGE and Coomassie Brilliant Blue staining. The molecular weights of the heavy (50 kDa) and light (25 kDa) chains of IgG are shown. (B) The inhibition of angiotensin-converting enzyme (ACE) 2 activity by 5 μg purified IgG was examined in triplicate assays. As a control, ACE2 activity in standard rACE2 was measured in the absence of IgG. As shown, ACE2 activity was significantly reduced when the recombinant enzyme was co-incubated with IgG from the patients. *P < 0.05, **P < 0.01. RFU, relative fluorescence unit.
Autoantibodies to ACE-2 in patients with CTD,
Takahashi et al, Arthritis Research and Therapy 2010
ROLE OF ENDOTHELIN-1

- Endothelin-1 is a potent vasoconstrictor, acts via ET-1 and ET-B receptors.
- Role being investigated in Diabetic nephropathy, lupus nephritis, cyclosporine induced renal failure.
- 10 times more vasoconstriction in renal bed compared to bronchial, femoral or coronaries.
- Kobayashi et al demonstrated positive staining for ET-1 and ET-B receptors in 2 patients with SRC. *Clinical Rheum, 1999*

*Figure 1. Plasma levels of endothelin-1 (ET-1) in patients with Raynaud’s phenomenon, as measured by sandwich enzyme immunoassay, in a group of young healthy female patients (Control 1; mean age 33), a group of middle-aged healthy women (Control 2; mean age 50), and in groups of patients with progressive systemic sclerosis (PSS; mean age 52), systemic lupus erythematosus (SLE; mean age 34), or mixed connective tissue disease (MCTD; mean age 35). Bars show the mean ± SD. NS = not significant.*

*Kazuhide, Arthritis and rheum, 1999*
SCLERODERMA RENAL CRISIS

- First described in 1863; Moore and Sheehan identified this as a major cause of death in scleroderma in 1960s.
- Cardinal features include: new onset significant systemic htn (>150/85mmHg) renal failure ( >30% decrease in egfr) MAHA, thrombocytopenia

--- Normotensive SRC

- Approximately 10% of patients with scleroderma have SRC; 12% in pts with dcSS, ~2% in pt’s with lcSS.
- 66% of cases occur < 1yr of onset; 75-80% of cases occur within 4yrs.
- Mortality in earlier case series was high as 50%; significant reduction after introduction of ace-i
Fig. 1. A potential pathogenetic mechanism for SRC with multiple factors contributing to a "vicious" cycle that results in malignant hypertension and renal failure.
Scleroderma renal crisis: pathology perspective, Batal et al, Int. j of Rheum 2010

-Gross pathology - multiple small petechial hemorrhages, tiny wedge shaped infarcts.

-Micros: vs malig htn/hus - more small vessel involvement than glomerular alteration.

-small vessel thrombi, onion skinning

-glomerulus-endothelial swelling, capil thrombus.

-c4d staining in PTC in pt’s with poor renal outcomes.
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Renal crisis (n = 195)</th>
<th>No renal crisis (n = 780)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>Symptoms less than 4 years</td>
<td>76%</td>
<td>78%</td>
</tr>
<tr>
<td>Race, % African American</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>25%</td>
<td>24%</td>
</tr>
<tr>
<td>Diffuse scleroderma (at renal crisis)</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>Anti-topoisomerase I antibody</td>
<td>20%</td>
<td>33%</td>
</tr>
<tr>
<td>Anti-polymerase III antibody</td>
<td>68% (n = 56)</td>
<td>44% (n = 237)</td>
</tr>
<tr>
<td>Anti-U3 RNA antibody</td>
<td>14% (n = 51)</td>
<td>15% (n = 211)</td>
</tr>
<tr>
<td>Anti centromere antibody</td>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings at time of renal crisis (or first visit)</th>
<th>Renal crisis (n = 195)</th>
<th>No renal crisis (n = 780)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, mean</td>
<td>184/108</td>
<td>120/74</td>
</tr>
<tr>
<td>Papilledema</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Seizures</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>24-hour protein, &gt;0.250gm/24 hours</td>
<td>63%</td>
<td>9%</td>
</tr>
<tr>
<td>Hematuria, RBC &gt;5/hpf</td>
<td>38%</td>
<td>2%</td>
</tr>
<tr>
<td>Granular casts</td>
<td>29%</td>
<td>1%</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia</td>
<td>30%</td>
<td>4%</td>
</tr>
<tr>
<td>Platelets &lt;150,000</td>
<td>39%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ESR &gt;25</td>
<td>61%</td>
<td>53%</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>53%</td>
<td>12%</td>
</tr>
<tr>
<td>CHF/arrhythmias</td>
<td>25%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Abbreviations: CHF, congestive heart failure; ESR, erythrocyte sedimentation rate; hpf, high-power field; RBC, red blood cell count.*
CLINICAL FEATURES AND ANTIBODY ASSOCIATION

- Headaches
- Blurry vision due to hypertensive retinopathy
- Encephalopathy
- Pulmonary edema
- Myocarditis
- Pericarditis
- Arrhythmia
- MAHA, thrombocytopenia, rising s.cr
- u/a- hematuria, mild proteinuria
- ANA -100%
  Strong association with speckled pattern.
  - Anti-fibrillarin or anti-U3RNP antibody-young people at risk for developing SSRc
  - Anti-centromere ab and anti-topoisomerase-lower risk

Rheumatology 2009, Denton et al
Poor outcome – male gender, age > 53yrs, rapidly progressive skin thickening
NORMOTENSIVE SRC

- “normal bp’ in the setting of other c/f of SRC like worsening s.cr/MAHA/thrombocytopenia; 5% - 10% of pts
- Some studies indicate that bp in these patients are higher than their baseline.
- Management includes Ace-I as tolerated by bp.

Retrospective study, 50 pts with SRC(1979-2003): 10 had normotensive SRC; 4 were already on Ace-I

MANAGEMENT

- Prior to Ace-I -b/l nephrectomies to manage malignant hypertension a/w high renin, survival < 10% after first year
- Role of Ace-I was first described in SRC by Wasner et al, series of 3 patients with SRC who survived 4-10yrs with captopril
- Key is to start Ace-I as soon as the diagnosis is made, continued despite rising s.cr.
- No difference in outcome in pt’s who were treated with Captopril vs other Ace-I.
- Transplant listing should be done if no improvement in renal function after 18months.
- Use of statins in alongside Ace-i- endothelial protection.

*Medical management of Scleroderma, Cannon, NEJM 1978*
*Successful Medical treatment of SRC, Wasner et al, Nejm 1978*
*Scleroderma renal crisis, Steen, 2009*
Use of ARB in SRC

- Steen et al – described a case series of patients of pts with SRC (n=10)
  - Initial treatment of choice was ARB
  - Switched from Ace-I to ARB due to intolerance to Ace-I
  - Addition of ARB to a regimen with Ace-I
  - Reported worsening hypertension and renal failure, including initiation of dialysis
  - Postulation was absence of bradykinin effect that occurs with ARB

- *Scleroderma Renal Crisis, Steen; Rheum Dis Clin N.Amer, 2009*
N=145 pts, Univ. of Pittsburgh

Scleroderma Renal Crisis, Steen ; Rheum Dis
Clin N.Amer
Role of Endothelin -1 receptor antagonist

60 yo woman with diffuse SSc/htn/hld with SRC, bp 150/80, s.cr 1.3 (0.9)
-intolerant to Ace-I
-home med included ibesartan 300mg, nifedipine, prednisone
-Diagnosis was confirmed by biopsy.
-Selective ET-a receptor antagonist Sitadsentan initiated for PAH (pap-100mhg)

*Endothelin Receptor antagonism and renin inhibition as treatment options for Scleroderma kidney, Dhaun, AJKK 2009*
Role of transplant

After adjusting for various factors like age, hla matching etc graft survival in pt’s with SSc was similar to those with DM-1; worse than DM-2/Sle

*Relationship between underlying renal disease and renal transplantation, Bleyer, AJKD 2001*
THANK YOU