Pericardial Disease in ESRD

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Background

- Uremic pericarditis
  - Clinical manifestations of pericarditis before renal replacement therapy or within 8 weeks of its initiation
- Dialysis pericarditis
  - Clinical features of pericarditis that develop after being stabilized on dialysis (>8 weeks after its initiation)
- Incidence
  - Historically, prior to the availability of dialysis, approximately 50% of patient who died of complications of uremia were found to have pericarditis on autopsy
  - Uremic: ranging from 3 to 41%, with most below 20%
  - Dialysis: 2 to 21%
- More common in:
  - Younger patients
  - Women > men
Clinical Features

• Symptoms:
  • Thoracic pain – most common, 40-100% of patients
  • Cough
  • Dyspnea
  • Malaise
  • Fever/chills
  • Weight loss
  • Asymptomatic in 8-30% of cases

• Physical signs:
  • Pericardial rub (59-100%)
  • JVD
  • Hypotension

• Laboratory findings:
  • Leukocytosis, elevated ESR
  • CXR – Cardiomegaly, concurrent pleural effusions (50%)
  • EKG – Classic finding of diffuse ST elevations are rare; more commonly, non-specific repolarization changes are noted
Differential Diagnosis

- Infectious
  - Viral (HIV, CMV)
  - Bacterial (tuberculosis)
  - Fungal
- Inflammatory
  - SLE
  - Scleroderma
  - ANCA-associated vasculitis
- Metabolic
  - Hypothyroidism
- Neoplastic
  - Metastatic
  - Primary
- Trauma
  - Idiopathic (procedures)
  - Blunt or penetrating
- Cardiac
  - Post-MI (Dressler’s syndrome)
- Medications
  - Hydralazine
  - Methyldopa
  - Procainamide
  - Minoxidil
Pathology

- Pericardial fluid is exudative and contains inflammatory cells (usually mononuclear with lymphocytic predominance)
- Fibrinous pericarditis is most common
- Serous or hemorrhagic fluid can also be seen
- Adhesive pericarditis from fibrinous adhesions are often present
Etiology

- Thought to be secondary to a uremic toxin
- Supported by the fact that uremic pericarditis responds very well to initiation of dialysis (> 76% of cases)
- In the past, metabolic derangements such as hyperparathyroidism, hypercalcemia, and hyperuricemia were implicated (no evidence)
- Volume overload may also play a role

- Is Dialysis pericarditis from a different etiology?
  - It responds less well to intensified dialysis
  - Some people have proposed that it is a reaction to something specific to dialysis itself (materials from dialyzers, tubing, dialysate, or contaminants from water have been implicated), but would be more widespread
  - Thought to be secondary to inadequate dialysis in stable pts or relatively inadequate dialysis in patients with comorbidites that increase catabolism
  - The resistance to intense dialysis may be because of a more prolonged period of asymptomatic or subacute presentation, leading to fibrosis and adhesions
Antunes, et al:

- Cross-sectional study of 34 patients on peritoneal dialysis
- No symptoms of pericarditis or effusions
- Five patients found to have asymptomatic pericardial effusion by TTE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>CI (95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male vs. female)</td>
<td>0.233</td>
<td>0.023-2.349</td>
<td>0.217</td>
</tr>
<tr>
<td>Age (per 1 year)</td>
<td>0.957</td>
<td>0.898-1.020</td>
<td>0.180</td>
</tr>
<tr>
<td>Diabetes mellitus (presence vs. absence)</td>
<td>1.481</td>
<td>0.210-10.46</td>
<td>0.693</td>
</tr>
<tr>
<td>Renal disease cause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>1.273</td>
<td>0.096-16.8</td>
<td>0.855</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>1.750</td>
<td>0.128-23.7</td>
<td>0.674</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.000</td>
<td>0.0-24</td>
<td>0.999</td>
</tr>
<tr>
<td>Others (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time on PD (per 1 month)</td>
<td>0.980</td>
<td>0.927-1.037</td>
<td>0.489</td>
</tr>
<tr>
<td>Peritoneal transport rate (high vs. low)</td>
<td>0.444</td>
<td>0.041-4.820</td>
<td>0.505</td>
</tr>
<tr>
<td>SBP (per 1 mm Hg)</td>
<td>1.008</td>
<td>0.952-1.067</td>
<td>0.786</td>
</tr>
<tr>
<td>DBP (per 1 mm Hg)</td>
<td>1.063</td>
<td>0.971-1.163</td>
<td>0.185</td>
</tr>
<tr>
<td>RRF (presence vs. absence)</td>
<td>0.675</td>
<td>0.096-4.766</td>
<td>0.693</td>
</tr>
<tr>
<td>BMI (per 1 kg/m²)</td>
<td>0.866</td>
<td>0.669-1.222</td>
<td>0.277</td>
</tr>
<tr>
<td>P3 phase angle (per 1°)</td>
<td>0.236</td>
<td>0.057-0.984</td>
<td>0.048</td>
</tr>
<tr>
<td>ECW/TBW (per 1 unit)</td>
<td>22</td>
<td>0.094-25</td>
<td>0.082</td>
</tr>
<tr>
<td>Albumin (per 1 g/dL)</td>
<td>0.215</td>
<td>0.024-1.932</td>
<td>0.170</td>
</tr>
<tr>
<td>Creatinine (per 1 mg/dL)</td>
<td>1.024</td>
<td>0.85-1.234</td>
<td>0.800</td>
</tr>
<tr>
<td>Urea (per 1 mg/dL)</td>
<td>1.006</td>
<td>0.976-1.037</td>
<td>0.714</td>
</tr>
<tr>
<td>Hb (per 1 g/dL)</td>
<td>0.451</td>
<td>0.275-0.913</td>
<td>0.027</td>
</tr>
<tr>
<td>Calcium (per 1 mg/dL)</td>
<td>0.424</td>
<td>0.126-1.428</td>
<td>0.166</td>
</tr>
<tr>
<td>Phosphorus (per 1 mg/dL)</td>
<td>1.401</td>
<td>0.759-2.584</td>
<td>0.281</td>
</tr>
<tr>
<td>PTH (per 1 pg/dL)</td>
<td>1.002</td>
<td>0.999-1.005</td>
<td>0.133</td>
</tr>
<tr>
<td>CRP (per 1 mg/dL)</td>
<td>1.008</td>
<td>0.621-1.636</td>
<td>0.973</td>
</tr>
<tr>
<td>Peritoneal Kt/V (per 1 unit)</td>
<td>0.334</td>
<td>0.029-3.782</td>
<td>0.376</td>
</tr>
<tr>
<td>Residual renal Kt/V (per 1 unit)</td>
<td>0.183</td>
<td>0.012-2.624</td>
<td>0.211</td>
</tr>
<tr>
<td>Total Kt/V (per 1 unit)</td>
<td>0.001</td>
<td>0.000-0.392</td>
<td>0.922</td>
</tr>
</tbody>
</table>

Resistance to EPO

- Case report of a 47 year old man with ESRD on HD for > 1 yr
- Initially Hgb > 30 without EPO
- Dialysis prescription was modified because of hypotension; Kt/v < 1.0
- Developed worsening anemia, need for EPO, with increasing requirements
- CRP concurrently rising
- Later, developed chest pain/SOB, diagnosed with pericardial effusion
- Treated with intensified dialysis
- EPO requirements decreased

Fig. 1. Changes in levels of haematocrit, plasma C-reactive protein, serum ferritin, and endogenous serum erythropoietin before, during, and after the occurrence of uraemic pericarditis.

Tarng, et al. NDT 1997; 12: 1051-1054
Overview of Management

- Intensive dialysis
- Steroids
  - Systemic
  - Intrapericardial
- NSAIDs
- Colchicine
- Surgical interventions
Intensive Dialysis

- Most people propose a trial of intensive dialysis if there is no evidence of hemodynamic compromise
- Daily, 4-hour dialysis sessions for a period of 10-14 days
- Response rates:
  - > 76% in uremic pericarditis
  - As low as 20% and up to 66% in dialysis pericarditis
  - Recurrence rates of 15%
- One study came up with a model to predict patients who would fail treatment with dialysis alone, who might benefit from early invasive procedures:
  - Fever >102, leukocytosis with WBC > 15,000 and left shift, treatment with only peritoneal dialysis, and the presence of a large effusion
  - Never validated
- Avoidance of anti-coagulation with heparin to prevent hemorrhagic conversion
- Repeat echocardiogram every 3-5 days to assess response
Tseng, et al

- Observational study of 88 patients with dialysis pericarditis who were treated with intensive dialysis, stratified by diabetic status
- 47 diabetic and 41 non-diabetic patients, between 2002-2006
- Intensive dialysis defined as daily dialysis for 10-14 days

### Table 4. Treatment modalities and outcomes of the study population (n = 88)

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Diabetics (n = 47)</th>
<th>Non-diabetics (n = 41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive hemodialysis</td>
<td>47 (100)</td>
<td>41 (100)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Resolution rate after intensive hemodialysis</td>
<td>40 (85.1)</td>
<td>34 (82.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>47 (100)</td>
<td>41 (100)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>8 (17.0)</td>
<td>7 (17.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pericardiocentesis</td>
<td>4 (8.5)</td>
<td>3 (7.3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Surgical drainage</td>
<td>3 (6.4)</td>
<td>4 (9.8)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Short-term outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive without recurrence</td>
<td>40 (85.1)</td>
<td>36 (87.8)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Alive with recurrence</td>
<td>2 (4.3)</td>
<td>2 (4.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Time to recurrence, days</td>
<td>578 ± 216.4</td>
<td>111.5 ± 13.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>5 (10.6)</td>
<td>3 (7.3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Time to mortality, days</td>
<td>10.2 ± 11.5</td>
<td>15.3 ± 10.7</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
Table 5. Analysis of the adequacy of dialysis (Kt/V) of the study population, stratified according to diabetic status (n = 88)

<table>
<thead>
<tr>
<th></th>
<th>Diabetics (n = 47)</th>
<th>Non-diabetics (n = 41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kt/V before intensive hemodialysis</td>
<td>0.97 ± 0.10</td>
<td>0.98 ± 0.12</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Kt/V after intensive hemodialysis</td>
<td>1.22 ± 0.11</td>
<td>1.22 ± 0.14</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 6. Analysis of the adequacy of dialysis (Kt/V) of the study population, stratified according to response status following intensive hemodialysis (n = 88)

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 74)</th>
<th>Non-responders (n = 14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kt/V before intensive hemodialysis</td>
<td>0.97 ± 0.11</td>
<td>0.97 ± 0.12</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Kt/V after intensive hemodialysis</td>
<td>1.25 ± 0.09</td>
<td>0.97 ± 0.09</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Oral Steroid Therapy

• Initial trial in 1971 by Compty, et al of 8 patients treated with 20 to 60mg of Prednisone daily for 1 to 12 weeks
  • 7/8 patients showed clinical improvement within 1-3 weeks
  • However, several patients had complications (infection)

• Subsequently, several case reports and series showed benefit
• However, there was also a high rate of recurrence

• Consensus is that systemic use is limited by potential for adverse effects and high risk of recurrence
Intrapericardial Steroids

- Intrapericardial instillation of a long-acting, nonabsorbable glucocorticoid into the pericardial sac via pericardiocentesis
- In 1978, Buselmeier, et al reported on 45 pts who had been refractory to treatment (intensified dialysis, anti-inflammatory medications)
  - 100mg of Triamcinolone hexacetomide injected q 4-6 hrs over 1-2 days
  - 45/46 patients responded, with no recurrences in average follow-up period of 14 months
  - One pt developed an asymptomatic internal mammary artery fistula as a result of needle insertion; otherwise no significant adverse events reported
- Subsequent studies, mostly small case series (7-17 pts each) showed similar results
- Limitation is the potential complications: infection, hemothorax, pneumothorax, arrhythmias, pneumopericardium
NSAIDs: Indomethacin

- A prospective, randomized controlled trial
- 24 patients with ESRD and uremic pericarditis
- Randomized to receive Indomethacin 25mg PO q6h vs placebo; treatment period of 3 weeks
- 21 pts were already on dialysis at the time of the study: no change in dialysis regimen; 3 pts were initiated on dialysis
- Results: Only significant difference between groups was duration of fever

Table 2. Early sequellae of uremic pericarditis in patients receiving indomethacin or placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Surgical interventiona</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>1b</td>
<td>2c</td>
</tr>
</tbody>
</table>

*a Pericardectomy or pericardiocentesis was used.

b No evidence of pericarditis was exhibited at the time of death.

c Both patients had clinical evidence of pericarditis at the time of death, but died of other causes.

Spector, et al. KI 1983; 24: 663-669
Fig. 1. Duration of pericardial friction rub and pain in dialysed patients with pericarditis. Each bar represents one patient. Bars followed by "S" or "†" represent patients requiring surgical intervention, or dying, on the post-treatment day indicated.

Fig. 2. Size of pericardial effusion, by echocardiogram, at entry into protocol and at 4 weeks. Each set of two circles represents a single patient. Points followed by "S" or "†" represent size of effusion at surgical intervention or death, respectively. For definitions of volume of pericardial effusion, see Results.
Colchicine

- Numerous cases reported in the literature of non-uremic pericarditis successfully treated with Colchicine
- Not extensively studied in uremic pericarditis
- Case report in NDT in 2004:
  - 48 yo woman with ESRD 2/2 PKD on HD who developed pericardial effusion
  - Resistant to intensified dialysis x 3 weeks
  - Responded to Methylprednisolone 40mg/d, but with recurrence
  - Refractory to second course of steroids
  - Treated with Colchicine 2mg daily x 5 weeks, then 1mg/d and 0.5mg/d, for total of 18 months
  - Effusion regressed starting at 7 weeks; at month 36, still in remission
- Proposed mechanism: via anti-inflammatory effects – binds to tubulin, blocks mitosis, and inhibits a variety of functions of polymorphonuclear leukocytes

Spaia, NDT 2004; 19: 2422
Surgical Interventions

- **Pericardiocentesis**: insertion of a needle into the pericardial sac to aspirate fluid
  - Effective, but recurrence is common
- **Pericardiotomy**: surgical incision of the pericardium, usually with installation of a drainage tube (pericardiostomy), +/- steroids
- **Pericardiectomy**: surgical removal of part of most of the pericardium
  - Usually performed via left anterior thoracotomy
  - Definitive procedure with low risk of recurrence
- **Pericardical window**: incision in the pericardium, with a drain placed to suction
  - Can either be done from subxiphoid approach, or less commonly, by a left thoracotomy, with the window placed to drain into the left pleural space and a chest tube placed to drain the fluid
Figueroa, et al

• An observational study of 57 patients with ESRD and pericardial effusions who were treated with surgical interventions between 1980 and 1991
• Seven patients had pericardiectomy via left thoracotomy under general anesthesia in the first two years
  • Patients did well, but required ICU stays post-operatively
• Subsequently, 52 patients underwent subxiphoid pericardial window (all but 5 with only local anesthesia)
  • Pericardial drainage tubes were placed surgically and removed after 4-5 days
  • Just as successful: no recurrence of effusions in any of the patients, without the increased risk of general anesthesia and minimal morbidity associated with the surgery
• Unclear why it works so well; it is postulated that drainage of the effusion enable adherence of the visceral and parietal surfaces, preventing fluid accumulation
Surgical interventions, cont’d

• Indicated without a trial of dialysis in patients with large effusions or those with any sign of hemodynamic compromise/tamponade

• No consensus about the timing or the preferred type of invasive intervention for the treatment of dialysis-associated pericardial effusions without tamponade

• Controversy regarding early intervention versus conservative intensive dialysis therapy remains
Thank you