Scleroderma renal crisis: a rare complication of systemic sclerosis with poor prognosis – experience in a medical center in central Taiwan

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Objective: Scleroderma renal crisis (SRC) is the most life-threatening complication of systemic sclerosis (SSc), which is characterized by malignant hypertension and rapidly progressive renal failure. In this study, we investigate the incidence, clinical features, treatment and outcome of our SRC patients.

Patients and Methods: We reviewed the records of 161 patients with SSc, seen from January 1991 to December 2005 in the Department of Rheumatology, Taichung Veterans General Hospital, Taiwan. Tests for anti-nuclear antibodies (ANA) in sera were screened against Hep-2 cells by indirect immunofluorescence assay. Quantification of autoantibodies to extractable nuclear antigen, including anti-Scl-70 antibody (Scl-70) and anti-centromere antibody, were tested with the AtheNa Multi-Lyte ANA test system. Data collected from the records included gender, age at onset, age at diagnosis, clinical manifestations, laboratory data, treatment and outcome. Fisher’s exact test was used to compare differences in categorical variables.

Results: Seventy-eight (48.4%) patients were limited type SSc and 83 (51.6%) patients were diffuse type SSc. Four (2.5%) patients of a total of 161 patients had SRC. All of our SRC patients were diffuse type with positive Scl-70. SRC occurred at 37.7 ± 55.72 months (range from 1-120 months) after the diagnosis of SSc. The duration between Raynaud’s phenomenon to disease onset was 3.75 ± 2.06 months. There were significant difference at myocardial involvement (p<0.05) and pericardial effusion (p<0.05) between the SRC and Non-SRC diffuse SSc patients. Two patients died within four months after the SRC, one patient required permanent dialysis and one patient partly regained renal function.

Conclusion: SRC is a rare complication in Taiwanese SSc patients and has a poor prognosis. Whether early administration of angiotensin converting enzyme inhibitor might prevent or ameliorate the onset of SRC needs further investigation.

Key words: Scleroderma renal crisis, anti-Scl-70 antibody, complications, prognosis

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by diffuse fibrotic and degenerative change in vessels, skin and internal organs [1]. Kidney involvement, as manifested by renal failure, was first described in SSc in 1863 [1]. The single most life-
threatening complication of this disease is scleroderma renal crisis (SRC) characterized by malignant hypertension and rapidly progressing renal failure [2]. Over the last few decades, the outcome of SRC patients has improved dramatically due to the introduction of angiotensin-converting enzyme inhibitors (ACEI) [3]. The incidence of SRC is estimated at around 10% in patients who have SSC and 25% in patients with diffuse types in Western countries [4], but figures have never been reported for Asian countries. In this study, we investigate and identify the clinical features, autoantibodies and prognosis of patients with SRC in central Taiwan.

Materials and Methods

Patients

In this retrospective analysis, 161 scleroderma patients who were treated in the Rheumatology Section of Taichung Veterans General Hospital from 1991-2005 were enrolled. All patients fulfilled the American College of Rheumatology classification criteria for SSc [5].

Laboratory and clinical assessments

Tests for anti-nuclear antibodies (ANA) in sera were screened against Hep-2 cells by indirect immunofluorescence assay. Quantification of auto-antibodies to extractable nuclear antigens (ENA), including anti-Scl-70 antibody (Scl-70) and anti-centromere antibody (ACA), was tested with the Athena Multi-Lyte ANA test system (Zeus Scientific, Orangeburg, SC, USA). Myocardial involvement was defined as one of the following: 1) left ventricular generalized hypokinesia; 2) left ventricular hypertrophy without systemic hypertension; 3) conduction defect, including bundle branch block, hemiblock, or ventricular dyssynchrony manifested by prolonged QRS duration >0.12 seconds; or 4) atrial or ventricular arrhythmia. Pericardial effusion was defined as moderate-to-massive pericardial effusion on echocardiogram. Interstitial lung disease was documented by pulmonary fibrosis confirmed by CXR and/or by high-resolution computed tomography (HRCT); exclusion of other known causes of interstitial lung disease.

Results

Seventy-eight (48.4%) patients were limited type SSc and 83 (51.6%) patients were diffuse type SSc. Only four (2.5%) patients out of a total of 161 patients had SRC, a figure that is considerably lower than those in the published data for Western countries [4]. All of our SRC patients were diffuse type with positive Scl-70 (Table 1). SRC occurred at 37.7 ± 55.72 months (range from 1-120 months) after the diagnosis of SSc. Poor prognosis was found in our SRC patients (two patients died of congestive heart failure, one patient required

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset</th>
<th>Sex</th>
<th>Time from Scleroderma to SRC (months)</th>
<th>Initial BP (SP/DP) mmHg</th>
<th>Cardiac failure</th>
<th>Intravascular hemolysis</th>
<th>Renal biopsy</th>
<th>Cr at onset of SRC (mg/dL)</th>
<th>Medication used prior to the onset of SRC</th>
<th>Daily dosage of ACEI (mg/day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>F</td>
<td>120*</td>
<td>180/110</td>
<td>No</td>
<td>No</td>
<td>ND</td>
<td>1.7</td>
<td>All drugs discontinued for six months</td>
<td>Fosinopril 40</td>
<td>Chronic renal insufficiency</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>F</td>
<td>3</td>
<td>200/105</td>
<td>Yes</td>
<td>Yes</td>
<td>ND</td>
<td>3.4</td>
<td>Pd 10 mg</td>
<td>Captopril 300</td>
<td>Dialysis</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>M</td>
<td>3</td>
<td>150/100</td>
<td>Yes</td>
<td>Yes</td>
<td>ND</td>
<td>2.4</td>
<td>Pd 15 mg</td>
<td>Fosinopril 40</td>
<td>Deceased</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>M</td>
<td>4</td>
<td>180/96</td>
<td>Yes</td>
<td>Yes</td>
<td>TMA</td>
<td>8.8</td>
<td>Pd 30 mg</td>
<td>Captopril 300</td>
<td>Deceased</td>
</tr>
</tbody>
</table>

Abbreviations: BP= blood pressure, SP = systolic pressure, DP =diastolic pressure, ND = not done, TMA = thrombotic microangiopathy, Cr = creatinine, Scl-70 = anti-Scl-70 antibody, Pd = prednisolone, DPCN = d-penicillamine, CyA = cyclosporin, MTX = methotrexate, Aza = azathioprine. Cyc = cyclophosphamide

*Patient 1 discontinued all medications and SRC occurred six months later.
and other antihypertensive agents. We observed that the duration between the onset of Raynaud’s phenomenon to SRC was 3.75 ± 2.06 months, which was shorter than for those patients without SRC. Patient 4 received renal biopsy which showed thrombotic microangiopathy (Figure 1), and fundus examination showed grade IV hypertensive retinopathy.

**Discussion**

The cause of discrepancy in the incidence of SRC between our SSc patients and those in Western countries is unknown (Table 2). Larger series have reported that the majority of SRC patients presented in the winter months [2,4]. Cannon et al. demonstrated that SRC patients had a significant reduction in renal cortical blood flow following the cold water-hand immersion test, suggesting that a cold environment is a major contributing factor in the development of SRC [6]. Because Taiwan is located in the subtropics and is relatively warm in the winter (a mean temperature of 15.4°C), we speculate that warm weather could serve as a factor for protecting Taiwanese SSc patients from developing SRC.

Three of our patients had taken cyclosporine, but discontinued it before the onset of SRC. Patient 2 and patient 3 received plamaphresis because of the mixed pictures of hemolytic uremic syndrome (HUS) and SRC. Though there have been case reports suggesting the efficacy of cyclosporine with regard to skin tightness [7-10], some authors reported the occurrence of SRC during cyclosporine therapy or immediately after discontinuance of the medication [11]. Furthermore, HUS has been widely described in transplant patients using cyclosporine. Taken together, we considered

### Table 2. Comparison of clinical features and laboratory characteristics in patients with scleroderma renal crisis (SRC) between studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Mean age at onset (years)</th>
<th>Frequency of SRC</th>
<th>Associated autoantibodies</th>
<th>Heart failure (%)</th>
<th>MAHA</th>
<th>Time from disease onset to develop SRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker [16]</td>
<td>Australia</td>
<td>54.5</td>
<td>2.8%</td>
<td>ANA-speckled pattern</td>
<td>56%</td>
<td>81%</td>
<td>15 months (1 week - 11 years)</td>
</tr>
<tr>
<td>Steen [1]</td>
<td>U.S.A</td>
<td>50.0</td>
<td>10.0%</td>
<td>Anti-RNA polymerase III antibodies</td>
<td>—</td>
<td>43%</td>
<td>75% less than 4 years</td>
</tr>
<tr>
<td>Penn [19]</td>
<td>United Kingdom</td>
<td>50.7</td>
<td>5.0%</td>
<td>Anti-RNA polymerase III antibodies</td>
<td>31%</td>
<td>59%</td>
<td>7.5 months (0 - 200 months)</td>
</tr>
<tr>
<td>Present study</td>
<td>Taiwan</td>
<td>52.0</td>
<td>2.5%</td>
<td>Anti-Scl-70 antibodies</td>
<td>75%</td>
<td>75%</td>
<td>37.7 months (1 - 120 months)</td>
</tr>
</tbody>
</table>

Abbreviations: ANA = antinuclear antibodies, Scl-70 = anti-Scl-70 antibodies, MAHA = microangiopathic hemolytic anemia
that although cyclosporine may have some beneficial therapeutic effects in SSc, the possibility of inducing SRC/HUS makes it a controversial treatment option.

This study also demonstrated that most of our patients developed SRC within 4 months after the diagnosis of SSc. Our findings were consistent with those of a previous study which indicated that new cardiac events [12], rapidly progressive skin disease [13] and diffuse skin disease [14] were risk factors for development of renal crisis (Table 3). However, there are some differences between our results and the published data. First, unlike patients in previous reports, all of our SRC patients had positive Scl-70 which is different from previous reports [15,16]. Possible protective effects of Scl-70 on the development of SRC were observed by Walker et al. [16]. However, recent studies have demonstrated that the Scl-70 can bind human fibroblasts and induce monocyte adhesion as well as activation [17]. It can also induce apoptosis and fibrillin 1 expression in human dermal endothelial cells [18]. These results support the theory that the Scl-70 is actively involved in the pathogenesis of fibrosis and endothelial damage in SSc patients rather than acting as a protective antibody. Furthermore, previous reports showed that 61% of patients had good outcome because they did not require, or only needed temporary dialysis [3]. Conversely, the prognosis was poor in our patient groups. Two patients died, one needed permanent dialysis and only one patient partially regained her renal function.

In conclusion, SRC is rare in Taiwanese SSc patients and has a poor prognosis. We may try cyclosporine in SSc patients, especially in those with high risk for developing SRC. Although ACEI has improved the outcome for patients in Western countries, it did not seem to be beneficial in our cohort. Whether early administration of ACEI might prevent or ameliorate the onset of SRC needs further investigation.

Table 3. Comparisons of clinical features and laboratory characteristics in patients with scleroderma renal crisis (SRC) and patients with non-SRC diffuse systemic sclerosis

<table>
<thead>
<tr>
<th></th>
<th>SRC (n = 4)</th>
<th>Non-SRC dSSc (n = 79)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at disease onset (years)</td>
<td>52 (40-64)*</td>
<td>51(14-83)*</td>
<td>NS</td>
</tr>
<tr>
<td>Duration from Raynaud’s phenomenon to disease onset (months)</td>
<td>2.5 (1-6)*</td>
<td>6.0 (0-180)*</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial involvement (%) (no. positive/no. tested)</td>
<td>100% (4/4)</td>
<td>41.4% (29/70)</td>
<td>0.036†</td>
</tr>
<tr>
<td>Pericardial effusion (%) (no. positive/no. tested)</td>
<td>50% (2/4)</td>
<td>4.8% (3/62)</td>
<td>0.026†</td>
</tr>
<tr>
<td>Interstitial lung disease (%) (no. positive/no. tested)</td>
<td>100% (4/4)</td>
<td>71% (51/71)</td>
<td>NS</td>
</tr>
<tr>
<td>Anti Scl-70 antibodies (%) (no. positive/no. tested)</td>
<td>100% (4/4)</td>
<td>74.7% (59/79)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Data: Median (range)
† Fisher’s Exact Test
NS = not significant

References
硬皮症腎臟危機：在中台灣硬皮症的一個罕見且預後不佳的併發症

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目的：在硬皮症的病人當中，腎臟危機是其中一個最具有致命性危機的併發症。它的特徵為惡性高血壓與快速的腎衰竭。在本研究當中，我們主要探討腎臟危機的發生機率，臨床特徵，治療與預後。方法與材料：自1991年至2005年當中，在本院過敏免疫風濕科共診斷的161例硬皮症病人。我們回溯性的去分析這些病人的性別，發病年紀，臨床特徵，實驗室數據特徵，治療與預後。結果：有78個病人屬於侷限型硬皮症(48.4%)，83個病人為瀰漫型硬皮症(51.6%)，共有4個病人發生腎臟危機(2.5%)。所有發生腎臟危機的病人都是屬於瀰漫型硬皮症的病人。血清中顯示全部都具有硬皮症抗體(anti-Scl-70 antibody)。在統計上發現腎臟危機與其他瀰漫型硬皮症的病人在心肌侵犯與心包膜積液有顯著差異。腎臟危機平均發生在硬皮症診斷37.7±55.7個月之後(範圍1-120個月)。這些病人發生雷諾氏現象到診斷硬皮症平均約為3.75±2.06個月。兩個病人在發生腎臟危機之後4個月內死亡，一個病人需要長期洗腎，只有一個病人恢復部分的腎功能。結論：硬皮症腎臟危機對於在中台灣的硬皮症病人是一個罕見的且預後不佳的併發症。對於早期給與血管緊張素轉化酶抑制劑是否能阻止硬皮症腎臟危機的發生仍需要進一步的研究。

關鍵詞：硬皮症腎臟危機，硬皮症抗體，併發症，預後