Assessment of kidney involvement

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ABSTRACT

Scleroderma renal crisis (SRC) represents the classic manifestation of kidney involvement in SSc. It particularly occurs in patients with early, rapidly progressive, diffuse skin involvement. Its detection requires the assessment of a few core set variables: arterial blood pressure, serum creatinine, and urinalysis. In clinical investigations SSc patients developing arterial hypertension after the disease onset (new onset hypertension) without SRC should also be reported.

Introduction

The classic kidney involvement in systemic sclerosis (SSc) is "scleroderma renal crisis" or SRC. Patients with diffuse cutaneous (dc) involvement, particularly those with early, rapidly progressive skin thickening and serum anti-RNA polymerase III antibody, are at highest risk to develop SRC. The typical presentation is that of a stable patient who abruptly develops severe arterial hypertension accompanied by headache, visual disturbance, seizures, congestive heart failure, pericardial effusion, microangiopathic hemolytic anemia, thrombocytopenia and accelerated oliguric renal failure (2). The optic fundi show acute hypertensive changes, including hemorrhages and exudates. Other findings include microscopic hematuria and proteinuria; occasionally RBC casts are seen in the urine. The plasma renin level is extremely high, as found in malignant essential hypertension. Renal biopsy characteristically shows changes in the small interlobular and arcuate arteries (2). The earliest change is intimal edema, followed by an intense proliferation of intimal cells and the production of mucinous ground substance composed of glycoprotein and mucopolysaccharide. Lymphocytes and other mononuclear cells are absent. On occasion fibrinoid necrosis may be present either in the arterial walls or in a subintimal location in small arteries and arterioles, but true vasculitis is rarely seen. Approximately 10% of SRC patients are normotensive. Antecedent corticosteroid use, especially prednisone 15 mg/day or greater (or the equivalent) is a risk factor for developing SRC.

Candidate variables

Although early studies suggested that 50% of patients with SSc had some type of renal abnormality, including proteinuria, hematuria, or decreased renal function, these findings in the majority of patients are explained by other illnesses, drug toxicities, or other scleroderma related problems (6). Some of these renal abnormalities occur in the setting of other severe SSc-related organ involvement such as heart failure or pulmonary hypertension, and thus do not represent primary SSc renal disease. There is no evidence that chronic, slowly progressive renal failure develops secondary to SSc.

Therefore, at this time the proposed criteria for documenting scleroderma renal involvement should include only abnormalities definitely or potentially related to SRC. If new data are published which indicate that other types of renal disease exist or more sophisticated renal function testing, which is reliable and valid, is predictive of outcome in patients with SSc the criteria proposed below should be appropriately revised.

The first class of renal involvement to be considered is arterial hypertension (systolic blood pressure >140 mmHg; diastolic blood pressure > 90 mmHg) that is not associated with other features of renal crisis (listed in Table I). Such "isolated" hypertension should be classified as occurring either antecedent to the onset of SSc or after the onset of SSc. The former is almost always "essential" hypertension while the latter, or "new onset" hypertension could be either essential hypertension or, more likely, SSc-related. This distinc-

tion will help future researchers to discern if non-SRC-related hypertension is an integral part of scleroderma or if it represents an early form of SRC.

As described above, renal crisis is a definite and usually easy to diagnose complication of SSc. It has features that are highly consistent from patient to patient. Since there is also a group of patients with renal crisis who do not have the typical features of malignant hypertension, "normotensive renal crisis" must also be defined. Even though standard blood pressure levels for definition as "hypertension" are not reached, a significant increase during the course of SSc in baseline blood pressure should be included in proposed criteria. However, these normotensive patients must have decrease renal function as measured by a serum creatinine along with at least one additional feature as described above that is not attributable to another disease. Table I summarizes the criteria for both hypertensive and normotensive renal crisis. Patients meeting either set of criteria will be classified as having SRC. Patients may also be deemed to have had a recurrence of SRC if they meet SRC criteria for a second time after a period during which SRC findings were absent (typically after treatment with ACE-inhibitors).

Table I. Criteria for scleroderma renal crisis as a renal manifestation of scleroderma. Definitions assume findings are not explained by other medical conditions

A. Hypertensive scleroderma renal crisis (fulfills both A1 and A2)

1. New onset hypertension; defined as any of the following:
   a) Systolic blood pressure ≥ 140 mg Hg
   b) Diastolic blood pressure ≥ 90 mg Hg
   c) Rise in systolic blood pressure ≥ 30 mm Hg
   d) Rise in diastolic blood pressure ≥ 20 mm Hg

AND

2. One (1) of the following five (5) features:
   a) Increase in serum creatinine by 50+% over baseline
   OR serum creatinine ≥ 120% of upper limit of normal for local laboratory
   b) Proteinuria ≥ 2+ by dipstick
   c) Hematuria ≥ 2+ by dipstick or ≥ 10 RBCs/HPF
   d) Thrombocytopenia: < 100,000 plts/mm^3
   e) Hemolysis defined as anemia not due to other causes and either of the following:
      (1) Schistocytes or other RBC fragments seen on blood smear
      (2) increased reticulocyte count

B. Normotensive scleroderma renal crisis (fulfills both B1 and B2)

1. Increase in serum creatinine >50% over baseline
   OR serum creatinine ≥ 120% of upper limit of normal for local laboratory

AND

2. One (1) of the following five (5) features:
   a) Proteinuria ≥ 2+ by dipstick
   b) Hematuria ≥ 2+ by dipstick or ≥ 10 RBCs/hpf
   c) Thrombocytopenia: < 100,000 /mm^3
   d) Hemolysis defined as anemia not due to other causes and either of the following:
      (1) Schistocytes or other rbc fragments seen on blood smear
      (2) Increased reticulocyte count
   e) Renal biopsy findings consistent with scleroderma renal crisis (microangiopathy)

Discussion

Identification of the core set variables

The presence, severity, or activity of renal involvement could include all renal findings attributed to SSc. One could consider serum creatinine, plasma renin level, urinalysis, 24-hour urine protein, 24-hour creatinine clearance, and hematologic parameters. Table II outlines the measures included in the core set for the detection of renal disease in SSc. The application of these core set measures should help to improve the comparability of clinical studies.

Table II. Core set variables.

A. Blood pressure; systolic and diastolic
B. Serum creatinine
C. Urinalysis; dipstick and microscopic

Rationale for the selection of the variables

The evaluation of arterial blood pressure and serum creatinine and urinalysis allow the clinical investigator to assess the presence of SSc kidney involvement (either hypertensive or normotensive SRC or new-onset hypertension). These measures are both reliable and feasible.

Rationale for the exclusion of other variables

Table III lists the variables not included in the core set. Although abnormalities in all of these variables are well documented in SSc, they may be due to other SSc organ system involvement or to a concomitant non-SSc disorder. For example, anemia can be due to bleeding from "watermelon stomach"; pro-

Table III. Other variables not incorporated in the core set.

A. 24-hour urine creatinine clearance
B. 24-hour urine protein
C. Platelet count
D. Schistocytes (peripheral blood smears)
E. Reticulocyte count
F. Hypertensive fundoscopic changes
G. Other manifestations of malignant hypertension (e.g.: encephalopathy)
H. Manifestations of uremia
I. Other studies of renal vascular function
J. Serum autoantibodies
K. Plasma renin level
L. Renal biopsy
M. Overlap renal syndromes (e.g., lupus nephritis)

teinuria can be attributable to D-penicillamine therapy; and thrombocytopenia may be detected in SSc patients without SRC. Thus, these individual parameters are not included in our criteria *per se* although many are inherent in the definition of SRC and hypertension. Additionally, independent renal disease such as ANCA-positive crescentic glomerulonephritis, which has been reported in SSc (7), or renal impairment that is part of an overlap syndrome (e.g. lupus nephritis) are not included. Scleroderma subsets (early rapidly progressive diffuse scleroderma) (8) and autoantibodies (anti-RNA polymerase III) (9) are predictors of renal crisis. However, since SRC is not seen exclusively in these patients, they are not useful as criteria.

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