Case Report

# Antineutrophil Cytoplasmic Antibody-Positive Crescentic Glomerulonephritis in Scleroderma — A Different Kind of Renal Crisis

DIANE L. KAMEN, FREDRICK M. WIGLEY, and ALAN N. BROWN

***ABSTRACT.*** Renal disease remains a major source of morbidity and mortality in patients with scleroderma (systemic sclerosis, SSc). We describe the clinical course of 3 patients with diffuse cutaneous SSc presenting with renal disease subsequently found to have antibodies to myeloperoxidase (anti-MPO) and crescentic glomerulonephritis. The presence of antineutrophil cytoplasmic antibodies (ANCA) and anti-MPO defines a subset of patients with SSc who are susceptible to crescentic glomerulonephritis. These patients may present in a manner identical to scleroderma renal crisis, yet treatment requirements differ significantly. We suggest that the presence of ANCA be routinely evaluated when faced with renal failure in the setting of SSc. (First Release July 1 2006; J Rheumatol 2006;33:1886–8)

*Key Indexing Terms:*
SCLERODERMA SYSTEMIC SCLEROSIS RENAL VASCULITIS

Renal involvement in scleroderma (systemic sclerosis, SSc) is classically characterized by malignant hypertension, elevated plasma renin, and rising serum creatinine reflective of worsening renal function, a constellation of findings referred to as scleroderma renal crisis (SRC)[1].

Circulating anti-myeloperoxidase (MPO) antibodies combined with a perinuclear staining pattern of antineutrophil cytoplasmic antibodies (p-ANCA) are considered to be highly specific markers for systemic vasculitis, particularly crescentic glomerulonephritis[2]. Anti-MPO antibodies can be found in a number of rheumatic diseases, but are rarely found in SSc[3-5]. In several case reports[6] high titers of p-ANCA in patients with SSc have been associated with rapid deterioration of renal function.

ANCA positivity and clinically evident vasculitis in patients with SSc with normotensive renal failure, often in the setting of pulmonary-renal syndrome, have been reported[6-9]. Additionally, cases to date in the literature describe a longer duration of SSc before onset of renal failure in ANCA-positive patients, in contrast to the typical presentation of SRC within the first 4 years of disease onset[1].

We describe 3 patients with SSc who each had presentations consistent with SRC, but were subsequently found to have anti-MPO antibodies and crescentic glomerulonephritis.

## CASE REPORTS

*Case 1.* A 45-year-old African American man presented with a 6-week history of chest discomfort and dyspnea and was found to have acute renal failure and anemia. He was in good health until 5 months prior to admission when he developed dysphagia to solids, a 70 lb weight loss, and Raynaud's phenomenon. Two months prior to presentation he noted skin tightening over his chest and hands. Review of systems was otherwise negative, including no fever, rash, sinus disease, hemoptysis, or neurologic deficits.

On admission, his blood pressure was 157/98 mm Hg. Examination revealed skin thickening over the hands, arms, face, and chest. His hands were puffy and digital pitted scars were noted. Nailfold capillaroscopy showed capillary dilatation, tortuosity, and wide areas of avascularity.

Urinalysis found > 300 mg/dl protein and 157 red blood cells (RBC) per high power field (hpf). A complete blood count was notable for a hemoglobin of 9.47 g/dl and platelet count of 395,000/mm$^3$. No microangiopathic changes were seen. Serum creatinine was 5.1 mg/dl and blood urea nitrogen (BUN) was 107 mg/dl.

Antinuclear antibody (ANA) and p-ANCA were positive by indirect immunofluorescence (IIF), at titers of 1:2560 and 1:80, respectively. Anti-MPO and Scl-70 antibodies were positive by ELISA, with an anti-MPO value of > 5 EU/ml being positive. Complements were normal. Anti-dsDNA, RNP, Sm, Ro, La antibodies were negative. Computed tomography (CT) of the chest showed pericardial and pleural effusions, but no evidence of vasculitis.

A 24-h urine collection contained 3.8 g of protein. Renal biopsy showed cellular crescents and necrosis without evidence of thrombotic microangiopathy or arterial narrowing (Figure 1). There was mild mucoid intimal thickening without onion-skinning. Immunofluorescence staining was negative for immunoreactants.

Treatment with high-dose corticosteroids was initiated, and oral

*From the Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, South Carolina, and the Division of Rheumatology, Johns Hopkins University, Baltimore, Maryland, USA.*

*Supported in part by the Multidisciplinary Clinical Research Center for the Study of Rheumatic Diseases in African-Americans (NIH).*

*D.L. Kamen, MD, Assistant Professor of Medicine; A.N. Brown, MD, Associate Professor of Medicine, Division of Rheumatology and Immunology, Medical University of South Carolina; F.M. Wigley, MD, Professor of Medicine, Division of Rheumatology, Johns Hopkins University.*

*Address reprint requests to Dr. D.L. Kamen, Division of Rheumatology, Medical University of South Carolina, 96 Jonathan Lucas Street, Suite 912, PO Box 250637, Charleston, SC 29425, USA.*
*E-mail: kamend@musc.edu*

*Accepted for publication April 7, 2006.*

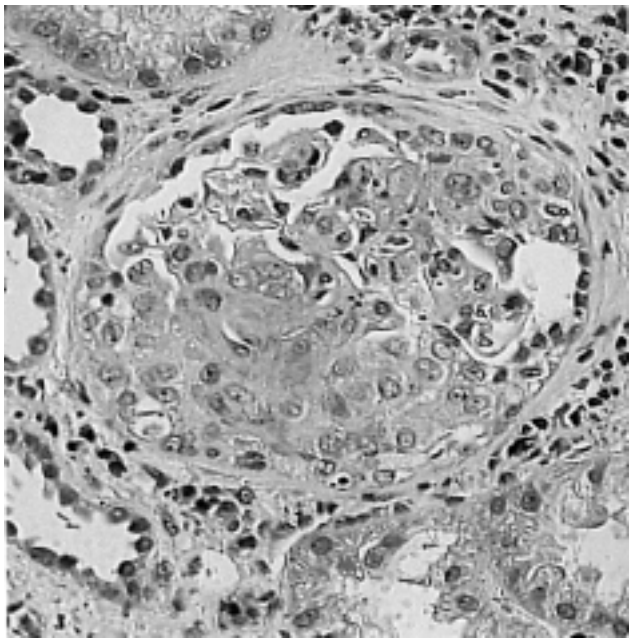

*Figure 1*. Renal histology from Case 1 showing large cellular crescent with necrosis and focal disruption of Bowman's capsule (H&E stain). There is no evidence of the juxtaglomerular cell hyperplasia or tubular cell flattening that can be seen with SRC. On electron microscopy (not shown), the glomerular basement membrane has normal thickness and contour, in contrast to the irregular thickening seen with SRC[1].

cyclophosphamide was given for 1 year. Two years later, he continues to require hemodialysis but has discontinued all immunosuppressant medications.

*Case 2*. A 19-year-old African American man, diagnosed 5 years previously with diffuse cutaneous SSc, presented with dyspnea. Review of systems was otherwise negative, including no constitutional symptoms, rash, sinus disease, hemoptysis, or neurologic deficits. In the past he had received hydroxychloroquine, D-penicillamine, infliximab, and cyclophosphamide for alveolitis and inflammatory myopathy. On presentation, creatinine had doubled from a baseline of 0.8 mg/dl to 1.6 mg/dl over 1 month. Blood pressure was 130/85 mm Hg, which was elevated from his baseline of 100/60.

Laboratory evaluation showed positive ANA at 1:2560 and positive Scl-70 antibodies. Anti-dsDNA, Ro, La, RNP, and Sm antibodies were negative. Urinalysis showed > 300 mg/dl protein, 109 RBC/hpf, 74 white blood cells/hpf, and 51 granular casts. The hematocrit was 29.5% and platelets 465,000/mm$^3$. p-ANCA was positive at a titer of 1:40 by IIF and anti-MPO antibodies were positive by ELISA at a value of > 5 EU/ml; complements were normal. CT scan of the chest showed bibasilar honeycombing unchanged from the CT 1 year prior, but no evidence of vasculitis.

A 24-h urine collection (240 ml) contained 921 mg protein. Renal biopsy showed a crescentic, proliferative glomerulonephritis. Arteries showed mild fibrous intimal thickening without onion-skinning. No thrombotic microangiopathy was seen and immunofluorescence staining was negative.

Despite treatment with hemodialysis, high-dose corticosteroids, and intravenous (IV) cyclophosphamide, his renal failure progressed and he expired shortly thereafter. No autopsy was performed.

*Case 3*. A 60-year-old Caucasian woman, with an 8-year history of diffuse cutaneous SSc, presented with a rising serum creatinine and active urinary sediment. Review of systems was otherwise negative, including no constitutional symptoms, rash, sinus disease, hemoptysis, or neurologic deficits. Three years previously, she had leg ulcers, and skin biopsy showed small/medium vessel vasculitis. Serological investigations were positive for p-ANCA at a titer of 1:160 and for anti-MPO antibodies at 75.3 units (positive > 20 units). She was treated with cyclophosphamide and corticosteroids, which had been discontinued 2 years prior to the current presentation.

Blood pressure was normal at 118/70 mm Hg. Skin changes typical for diffuse cutaneous SSc were noted. No skin ulcers were present.

Laboratory evaluation showed positive ANA and Scl-70 antibodies. Anti-dsDNA, Ro, La, RNP, and Sm antibodies were all negative. Urinalysis found 2+ protein and numerous granular and RBC casts. Hemoglobin was 10.2 g/dl, platelets were normal, and no microangiopathic changes were seen. BUN was 62 mg/dl with a creatinine of 2.2 mg/dl. p-ANCA was positive by IIF at a titer of 1:80 and anti-MPO antibodies were positive by ELISA at 32.9 units (positive > 20 units); complements were normal.

Renal biopsy showed a necrotizing and crescentic glomerulonephritis. No thrombotic microangiopathy, arterial narrowing, or intimal proliferation was seen. Immunofluorescence showed no significant immune complex deposition.

She was treated with high-dose corticosteroids and oral cyclophosphamide. Over the subsequent 2 weeks the creatinine fell from 4.0 to 1.7 mg/dl, and she improved clinically.

## DISCUSSION

In this case series we report that pauciimmune glomerulonephritis associated with anti-MPO antibodies can occur in patients with SSc and can simulate SRC. Our experience emphasizes the importance of carefully evaluating patients with SSc who present with acute renal failure for causes other than SRC. Consideration of other etiologies should not, however, delay the prompt initiation of angiotensin-converting enzyme (ACE) inhibitor therapy essential to the treatment of SRC. Early recognition of anti-MPO antibodies will define patients who may require renal biopsy and may respond to immunosuppressive therapy.

All of our cases had large proteinuria with hematuria or an active urinary sediment with casts, which are findings more typical of a glomerular process rather than a vascular process as seen in SRC. Renal biopsies also showed a primarily glomerular process with glomerular crescents and necrosis. Two of the 3 cases had intimal proliferation of renal vessels, which can occur in patients with diffuse cutaneous SSc without SRC[1], but they did not have the luminal occlusion or onion-skinning often seen in SRC.

There are other reports of anti-MPO associated glomerulonephritis in SSc, but these were almost exclusively associated with normotensive renal failure. Several of these cases developed renal disease in the setting of treatment with D-penicillamine[6-10]. Only our Case 2 had a short course of D-penicillamine, discontinued 4 years prior to the presentation with vasculitis. On review of the medication histories of our 3 cases, neither of the other 2 had been exposed to D-penicillamine, and no other medications linked to the development of vasculitis were found.

Case 3 is unique in that anti-MPO antibodies had been identified several years prior to the development of renal failure. This suggests that a positive ANCA in a patient with SSc may be a prognostic indicator warranting close observation for renal disease.

Endo and colleagues found 6 of 100 consecutive Japanese

patients with SSc to be positive for p-ANCA[6]. All 6 had renal failure and of the 3 with renal histology available, all had crescentic glomerulonephritis. They concluded that ANCA is a marker for a subset of patients with SSc with normotensive renal failure. In our case series, 2 patients were hypertensive at presentation. These findings suggest it is important to consider an ANCA-associated glomerulonephritis even in the setting of classic hypertensive SRC.

We recommend testing for ANCA as part of the routine evaluation of patients with SSc with suspected renal crisis or evidence of glomerular disease by urinalysis. If positive, a renal biopsy should be strongly considered. This approach will help to clearly define the underlying pathophysiologic process and guide subsequent therapy.


## ACKNOWLEDGMENT

The authors thank Dr. Richard M. Silver for his support in the preparation of this manuscript.


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