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Original contribution

Renal biopsy findings predicting outcome in scleroderma renal crisis☆

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Summary Scleroderma renal crisis is irreversible in some patients despite aggressive treatment. This study was designed to identify pathologic prognostic features in scleroderma renal crisis. We retrospectively reviewed the pathology and the clinical records of 17 patients who underwent kidney biopsies during scleroderma renal crisis (group A, recovered renal function [n = 7]; group B, remained in renal failure or died [n = 10]). Multiple histologic features were assessed semiquantitatively (0-3) or as percentages. C4d staining of peritubular capillaries and small vessels was assessed semiquantitatively (0-3) in patients with scleroderma (n = 11), normotensive (n = 10), and hypertensive (n = 12) nonscleroderma native kidney controls. The percentage of thrombosed vessels (25.1 ± 21.0 versus 5.6 ± 12.3, $P = .045$) and the severity of glomerular ischemic collapse (2.9 ± 0.3 versus 1.4 ± 0.8, $P = .001$) were significantly higher in group B than in group A. Also, group B patients tended to have more severe acute tubular injury and vascular fibrinoid changes. The peritubular capillary C4d score in patients with scleroderma, normotensive controls, and hypertensive controls were 1.1 ± 0.9, 0.3 ± 0.7, and 0.3 ± 0.5, respectively ($P = .018$, scleroderma versus other controls). Small vessel C4d score was higher in scleroderma compared to normotensive but not hypertensive controls. Within scleroderma samples, a significantly higher peritubular capillary C4d score (1.6 ± 0.7 versus 0.3 ± 0.5, $P = .024$) but not small vessel score was found in group B compared to group A. This tended to be associated with peritubular capillary leukocyte margination. Vascular thrombosis, severe glomerular ischemic collapse, and peritubular capillary C4d deposits in scleroderma renal crisis kidney biopsies correlated with increased risk of failure to recover renal function.

1. Introduction

Systemic sclerosis is a multisystem disorder affecting small blood vessels and connective tissues. Its standard classification is as diffuse cutaneous or limited cutaneous variants [1]. Scleroderma renal crisis (SRC) is a

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complication of systemic sclerosis that occurs in up to 10% of patients. SRC is typically characterized by the new onset of hypertension (although few patients remain normotensive) and acute renal failure, with or without evidence of microangiopathic hemolytic anemia or thrombocytopenia [2,3]. The mortality associated with SRC has diminished significantly because of early diagnosis and angiotensin-converting enzyme inhibitor therapy [4,5]. Nevertheless, some patients are refractory to angiotensin-converting enzyme inhibitor therapy and remain on dialysis or die [2,6,7].

Although many studies have been conducted to investigate its pathogenesis, the etiology of systemic sclerosis remains incompletely understood [8]. Some investigators believe that systemic sclerosis is a disorder of cell-mediated immunity [9,10]; some contend that antibody-mediated injury plays an important role [11], whereas others stress the importance of T cell–B cell interaction [1]. Patients with systemic sclerosis have expansion in naive B cells, decrease in memory B cells, and increase in CD19 expression. This may result in antibody production through inhibition of B-cell peripheral tolerance [12].

C4d is a classic pathway complement degradation product. Its presence is associated with antibody-mediated injury in renal allografts, and it has been shown to independently predict unfavorable renal allograft outcome [13-15]. Activated C4 is cleaved to C4a and C4b. C4b binds to amino or hydroxyl groups and is then converted to C4d, which can covalently bind to the peritubular capillary (PTC) basement membrane [16]. C4d staining pattern in SRC has not been investigated yet.

This study was designed to identify potential clinical and pathologic prognostic factors and to investigate C4d deposition in SRC.

2. Materials and methods

2.1. Study design

We retrospectively reviewed clinical and surgical pathology records of 17 patients with scleroderma who underwent native renal biopsies during SRC between 1990 and 2007, with the last clinical follow-up in October 2007. Fifteen patients with SRC were seen at the University of Pittsburgh Medical Center and met the original classification criteria proposed by the American College of Rheumatology [17] for systemic sclerosis and the recent revisions [18]. The remaining 2 patients had their biopsy specimens referred from an outside institution with the diagnosis of systemic sclerosis and worsening renal function. Ten specimens derived from nonneoplastic areas of kidneys resected for renal neoplasms and 12 from non-SRC patients with hypertension (5 idiopathic malignant hypertension and 7 chronic benign hypertension) were used as controls for C4d staining in native kidneys.

2.2. Histologic evaluation

Standard hematoxylin and eosin, periodic acid–Schiff, silver, and trichrome sections were evaluated. Histologic changes in all 4 renal anatomic compartments (glomeruli, tubules, interstitium, blood vessels) were assessed and scored semiquantitatively (0-3) or recorded as percentages. The glomerular alterations assessed included glomerular ischemic collapse, glomerular basement membrane (GBM) double contours (tram tracking), and juxtaglomerular apparatus (JGA) prominence. These changes were graded on a semiquantitative scale (0-3) according to the severity of the most affected nonsclerotic glomerulus. Glomerular ischemic collapse was graded as no (0), mild (1), moderate (2), or severe (3) glomerular collapse based on the most severely affected glomeruli. Glomerular double contour was graded from 0 to 3 when double contour lesion was seen in less than 10%, 11% to 25%, 26% to 50%, or more than 50% of capillary loops, respectively. JGA status was graded on a scale (0-3) corresponding to inconspicuous JGA, mild hyperplasia, moderate hyperplasia, and severe hyperplasia, respectively. Global glomerulosclerosis and glomerular thrombosis were recorded as a percentage of the number of affected glomeruli.

Tubular pathologic alterations were assessed. Acute tubular injury was graded on a semiquantitative scale based on the most affected area, corresponding to no injury (0), wrinkling of tubular basement membrane or tubular epithelial vacuolization (1), attenuation of tubular epithelium (2), and necrosis (3), respectively. Tubular atrophy was graded on a semiquantitative scale according to the cortical surface area involved by tubular atrophy: no atrophy (0), and atrophy involving up to 25% (1), 26% to 50% (2), and more than 50% (3) of cortical tubular profiles, respectively. Interstitial fibrosis was graded on a semiquantitative scale based on the cortical surface area involved, corresponding to less than 5% (0), 6% to 25% (1), 26% to 50% (2), and more than 50% (3), respectively.

Vascular abnormalities were separated into acute (vascular myxoid and fibrinoid changes), subacute (onion skin lesions), and chronic (fibroelastic intimal thickening, muscular thickening, and hyalinosis). Each abnormality was graded on a semiquantitative severity scale (0-3) based on the most severely affected vessel. Fibrinoid change was evaluated according to extension of this lesion within vascular wall as no fibrinoid alteration (0), fibrinoid change involving the intima up to the muscularis (1), through the muscularis (2), and the entire wall thickness (3). Onion skin lesion was evaluated according to the severity of proliferative endarteropathy and concentric fibrosis within the involved arteriole/ interlobular artery as no (0), early (1), well established (2), or advanced (3) onion skinning lesion. Fibroelastic intimal thickening and myxoid changes were graded on a scale (0-3) corresponding to no significant narrowing, narrowing of up to 25%, 26% to 50%, and more than 50% of luminal cross-sectional surface