

Pauci-immune Crescentic Glomerulonephritis Superimposed on Diabetic Glomerulosclerosis

Samih H. Nasr,* Vivette D. D'Agati,* Samar M. Said,* Michael B. Stokes,* Gerald B. Appel,[†] Anthony M. Valeri,[†] and Glen S. Markowitz*

*Department of Pathology and [†]Department of Medicine, Division of Nephrology, Columbia University, College of Physicians & Surgeons, New York, New York

Background and objectives: Pauci-immune necrotizing and crescentic glomerulonephritis (PNCGN) superimposed on diabetic glomerulosclerosis (DGS) is a rare occurrence. Only limited data on this dual glomerulopathy are available.

Design, setting, participants, & measurements: Twenty-three cases of PNCGN superimposed on DGS were identified from the archives of the Renal Pathology Laboratory of Columbia University. The clinical features, pathologic findings, and outcomes are described.

Results: The majority of patients were white, elderly, and had longstanding diabetes. Patients presented with acute renal failure and an active urine sediment. Antinuclear cytoplasmic autoantibody (ANCA) testing was positive by indirect immunofluorescence in 18 of 22 patients. Sixteen patients had a P-ANCA pattern, 9 of whom underwent further testing and were found to be MPO-ANCA positive by enzyme-linked immunosorbent assay. Among the two patients with C-ANCA by indirect immunofluorescence, enzyme-linked immunosorbent assay was performed in one and revealed PR3-ANCA. Eight patients had extrarenal manifestations of vasculitis, including 6 with pulmonary hemorrhage. At the time of presentation and renal biopsy, 11 patients required hemodialysis. The mean percentages of glomeruli with cellular crescents, fibrous crescents, and necrosis were 24.9, 8.4, and 12.9, respectively. Most patients were treated with cyclophosphamide and prednisone. At a mean follow-up of 14.6 mo (available in 21 patients), 8 patients had died and 8 of the remaining 13 patients had reached end-stage renal disease. Correlates of end-stage renal disease were hemodialysis at presentation and the degree of DGS.

Conclusions: PNCGN may occur superimposed on DGS. The prognosis for this dual glomerulopathy is dismal despite aggressive therapy.

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Diabetes mellitus (DM) is the most common cause of end-stage renal disease (ESRD) in the developed world. The majority of diabetic patients who develop proteinuria and renal failure have diabetic glomerulosclerosis (DGS), which is characterized by diffuse or nodular mesangial sclerosis and thickening of glomerular and tubular basement membranes. Given the likelihood of finding DGS, most patients with DM who develop proteinuria and renal insufficiency do not undergo renal biopsy.

Common indications for renal biopsy in patients with DM include sudden onset of heavy proteinuria, proteinuria in the absence of diabetic retinopathy, acute renal failure (ARF), and persistent hematuria (1). Arterionephrosclerosis, ischemic nephropathy, papillary necrosis, acute pyelonephritis, and glomerulonephritis are some of the more frequent nondiabetic conditions that occur in diabetic patients. The biopsy prevalence of nondiabetic diseases varies widely, from 6% to 81% (2),

depending on the threshold of nephrologists for performing renal biopsy on diabetic patients (1,3–4).

In diabetic patients, renal biopsy may reveal DGS, nondiabetic renal disease, or DGS with superimposed nondiabetic disease. Among the glomerular diseases that may occur superimposed on DGS, the most common are membranous glomerulopathy, IgA nephropathy, and acute postinfectious glomerulonephritis (1,2). Minimal change disease, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and lupus nephritis also have been reported. Rapidly progressive glomerulonephritis is a common pattern of ARF in older patients coming to renal biopsy. Nevertheless, pauci-immune necrotizing and crescentic glomerulonephritis (PNCGN) superimposed on DGS is a rare occurrence, with only 9 cases reported in the English literature (5–12). Herein, we describe the clinical, pathologic, and outcome data of 23 patients with PNCGN superimposed on DGS.

Materials and Methods

Twenty-three patients with renal biopsy findings of PNCGN superimposed on DGS were identified retrospectively from the Renal Pathology Laboratory files at Columbia University between 2000 and 2007.

All renal biopsies were processed according to standard techniques for light microscopy, immunofluorescence, and electron microscopy.

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Correspondence: Dr. Samih H. Nasr, Department of Pathology, Columbia University, College of Physicians & Surgeons, 630 West 168th Street, VC14–224, New York, NY 10032. Phone: 212-305-9669; Fax: 212-342-5380; E-mail: sn386@columbia.edu

For each case, 11 glass slides were prepared and stained with hematoxylin and eosin, periodic acid-Schiff, trichrome, and Jones methenamine silver. Immunofluorescence was performed on 3- μ m cryostat sections using polyclonal fluorescein isothiocyanate-conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinogen, and albumin (Dako Corporation, Carpinteria, CA). Ultrastructural evaluation was performed using JEOL 100S or 1010 electron microscopes (Tokyo, Japan).

Patients' medical records were reviewed for demographics, duration of diabetes, clinical features of systemic vasculitis, antinuclear cytoplasmic autoantibody (ANCA) specificity, parameters of renal function, treatment, and outcome. The following clinical definitions were applied: renal insufficiency, serum creatinine >1.2 mg/dl; nephrotic range proteinuria (NRP), 24 h urine protein \geq 3 g/d; hypoalbuminemia, serum albumin \leq 3.5 g/dl; nephrotic syndrome, NRP, hypoalbuminemia, and peripheral edema; hematuria, >5 red blood cells per high power field (HPF) on microscopic examination of the urinary sediment; and leukocyturia, >5 white blood cells per HPF. Hypertension was defined as a systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or the use of antihypertensive medications.

The degree of glomerulosclerosis was graded semiquantitatively on a scale of 0 to 3 according to the grading system of Gellman *et al.* (13), with modification as follows: mild, a single mesangial nodule in occasional glomeruli for cases of nodular DGS and focal and segmental mesangial sclerosis for cases of diffuse DGS; moderate, many glomeruli containing nodules for cases of nodular DGS and diffuse and global mesangial sclerosis for cases of diffuse DGS; and severe, almost every glomerulus contained one or more nodules for cases of nodular DGS and severe mesangial sclerosis with narrowing or occlusion of the glomerular lumina for cases of diffuse DGS. Similarly, tubular atrophy and interstitial fibrosis were graded on a semiquantitative scale based on an estimate of the percentage of renal cortex affected and recorded as: 0 (none), 1% to 25% (mild), 26% to 50% (moderate), or >50% (severe).

Statistical analysis was performed using SPSS for Windows (Chicago, IL). Continuous variables are reported as the mean \pm standard deviation. Analysis was performed using exact nonparametric tests, including (as appropriate for variable type) the Fisher exact test, the Wilcoxon rank sum test, and the Kruskal-Wallis test. Survival analysis (to the endpoint of ESRD) was performed using the Cox proportional hazard model (or Cox regression) with results reported as the hazard or odds ratio and the 95% confidence interval. For all tests, statistical significance was assumed at $P < 0.05$.

The study was approved by the Institutional Review Board of Columbia University Medical Center.

Results

Clinical Features

The clinical features are summarized in Table 1. The cohort consisted of 13 men (56.5%) and 10 women (43.5%) with a mean age of 64.2 yr (range, 28 to 82 yr). Only 5 patients (21.7%) were younger than 60 yr. Eighteen patients (78.3%) were white, 3 (13%) were black, and 2 (8.7%) were Hispanic. The mean duration of DM was 12.3 yr (range, 1 to 40 yr). Only 6 of 16 patients (37.5%) with available data had retinopathy. Eighteen patients (78.3%) had a history of hypertension.

ANCA serologies were positive in 18 of 22 patients (81.8%) tested by indirect immunofluorescence (IIF) (Table 2). Among the 16 patients (88.9%) with P-ANCA by IIF, enzyme-linked immunosorbent assay (ELISA) was performed in 9 patients, all

Table 1. Patient demographics (23 patients)

	No. (%) of patients
Male/female	13/10 (56.5/43.5)
Age (yr) (mean \pm SD)	64.2 \pm 13
28–50	4 (17.4)
51–60	2 (8.7)
61–70	9 (39.1)
71–82	8 (33.7)
Race/ethnicity	
white	18 (78.3)
black	3 (13.0)
Hispanic	2 (8.7)
Duration of diabetes	
<10 yr	7 (30.4)
>10 yr	13 (56.5)
unknown	3 (13.0)
Retinopathy	
yes	6 (26.1)
no	10 (43.5)
unknown	7 (30.1)
Hypertension	18 (78.3)

SD, standard deviation.

of whom were found to have MPO-ANCA. The remaining two patients had C-ANCA by IIF, one of whom underwent further testing and was found to have PR3-ANCA by ELISA. While six patients (26.1%) had evidence of pulmonary hemorrhage, one had cutaneous purpura, and one had recurrent episcleritis, the majority of patients had no extra-renal manifestations of vasculitis. Three patients were being treated for hypertension with hydralazine, including two for >1 yr and one for 2 wk. The remaining 20 patients were not receiving any medication that is associated with drug-induced ANCA.

All patients presented with ARF and active urine sediment, often superimposed on chronic kidney disease. At the time of presentation and renal biopsy, 11 patients (47.8%) required hemodialysis (HD). The mean serum creatinine at the time of biopsy in the remaining 12 patients was 4.1 mg/dl (range, 1.3 to 8.7 mg/dl). Baseline renal insufficiency was present in 11 of 19 patients (57.9%) with available data, and the mean baseline serum creatinine (before presentation) was 1.6 mg/dl. Proteinuria was documented in all patients, with a mean 24-h urine protein of 4.1 g in the 16 patients in whom data were available (range, 1.1 to 9.4 g). Eight of the 16 patients (50%) had NRP, including 5 (31.2%) with full nephrotic syndrome. The mean serum albumin was 3.1 g/dl (range, 1.8 to 4.2 g/dl), and peripheral edema was present in 13 patients (56.5%). All 22 patients with available urinalysis had microscopic hematuria, 12 (54.5%) had leukocyturia, and 5 (22.7%) had evidence of red blood cell casts.

Pathologic Features

The renal biopsy findings are detailed in Table 3. Sampling for light microscopy included a mean of 17.9 glomeruli (range,

Table 2. Clinical presentation (23 patients)

	No. of patients
ANCA status	
P-ANCA by IIF	16 (69.6%)
MPO ANCA by ELISA	9 of 9 (100%)
C-ANCA by IIF	2 (8.6%)
PR3 ANCA by ELISA	1 of 1 (100%)
negative	4 (17.4%)
not available	1 (4.3%)
Extrarenal manifestation of vasculitis	
none	15 (65.2%)
pulmonary hemorrhage	6 (26.1%)
episcleritis	1 (4.3%)
purpura	1 (4.3%)
24-h urine protein (g) ^a	4.1 ± 2.7 (1.1–9.4)
Serum albumin (g/dl)	3.1 ± 0.6 (1.8–4.2)
Edema	13 (56.5%)
Full nephrotic syndrome	5 of 16 (31.2%)
Hematuria	22 of 22 (100%)
Baseline serum creatinine (mg/dl) ^b	1.6 ± 0.7 (1.0–3.3)
On HD at biopsy	11 (47.8%)
Serum creatinine at biopsy in the 12 patients not on HD (mg/dl)	4.1 ± 1.9 (1.3–8.7)

ANCA, antinuclear cytoplasmic antibody; HD, hemodialysis; IIF, indirect immunofluorescence; MPO, myeloperoxidase; PR3, proteinase 3. Data are mean with range or fraction with corresponding percentage.

^aNot available in 7 patients, all of whom had 1–3+ protein on urinalysis.

^bAvailable in 19 patients.

4 to 41 glomeruli), and a mean of 26.9% of glomeruli were globally sclerotic. All biopsies revealed PNCNG superimposed on DGS. Crescents were present in all cases (Figure 1A and C), including cellular and fibrous crescents in 8 (34.7%), exclusively cellular crescents in 14 (60.8%), and exclusively fibrous crescents in 1 (4.3%). Cellular and fibrous crescents involved a mean of 24.9% and 8.4% of glomeruli, respectively. Seventeen cases (73.9%) showed segmental necrotizing features characterized by endocapillary and extracapillary fibrin, glomerular basement membrane (GBM) rupture, and neutrophil infiltration and karyorrhexis (Figure 1B). The necrotizing features involved a mean of 12.9% of glomeruli (range, 0% to 53%) and frequently were found in glomeruli with cellular crescents. All biopsies showed features of DGS, including mesangial sclerosis and thickening of glomerular and tubular basement membranes. The pattern of DGS was diffuse in 16 patients (69.6%) and nodular in 7 (30.4%). The degree of DGS ranged from mild (52.2% of cases) to moderate (39.1%) to severe (8.7%). All cases showed interstitial inflammation, which ranged from focal (60.9%) to diffuse (39.1%). The degree of tubular atrophy and interstitial fibrosis ranged from mild (21.7%) to moderate (47.8%) to severe (30.4%). Arteriosclerosis and arteriolar hyalinosis were present in all but one case and in the majority of cases were of at least moderate severity (91.3%). Necrotizing vasculitis was seen in only one biopsy.

Immunofluorescence was performed on all biopsies and commonly revealed low intensity linear staining of glomerular

and tubular basement membranes for IgG and albumin, which is a common finding in DGS. Staining for fibrinogen highlighted areas of glomerular fibrinoid necrosis. As expected for a pauci-immune disease process, none of the biopsies exhibited findings suggestive of glomerular immune deposit formation.

Electron microscopy was performed in 20 of the 23 cases and revealed findings typical of DGS. Electron dense deposits were not identified in 18 of the 20 biopsies (90%). In the remaining 2 cases, rare, minute subepithelial deposits were seen at the GBM reflection over the mesangium. The mean degree of foot process effacement was 52% (range, 10% to 100%).

Outcome

Clinical follow-up was available for 21 patients (91.3%) (Table 4). Induction therapy consisted of steroids and cyclophosphamide (CYC) in 14 patients (12 with oral CYC; 2 with intravenous CYC), steroids and mycophenolate mofetil in 1, steroids and azathioprine in 1, steroids and methotrexate in 1, and steroids alone in 2. In addition to immunosuppressive therapy, 5 patients (23.8%) underwent plasmapheresis. The remaining 2 patients did not receive immunosuppressive therapy because of concurrent sepsis in 1 and advanced tubulointerstitial scarring on renal biopsy in the other. After receipt of the renal biopsy results, hydralazine was discontinued in 2 of the 3 patients who were on this medication.

The mean duration of follow-up for the 21 patients was 14.6 mo (range, 1 wk to 92 mo). Among the 21 patients, 8 (38.1%) died and the mean interval from biopsy to death was 6.1 mo (range, 1 wk to 25 mo). The cause of death was sepsis in 4 patients, myocardial infarction in 1, and undetermined in 3. Eight of the remaining 13 patients reached ESRD (61.5%), including 3 who received renal transplants and had excellent graft function.

Among the 11 patients who were on HD at the time of presentation, 9 (81.7%) remained HD-dependent. Among these 9 patients, one was able to transiently discontinue HD. The remaining 2 patients discontinued HD and had creatinines of 3.0 and 3.5 mg/dl at a mean of 7-mo postrenal biopsy. Among the 10 patients who did not require HD at the time of presentation, 3 (30%) became HD-dependent at a mean of 4.5 mo postbiopsy. The remaining 7 patients have persistent renal insufficiency with a mean creatinine of 2.26 mg/dl at a mean of 9.3-mo postrenal biopsy. None of the 7 patients had a decline in serum creatinine to baseline level.

Correlates of ESRD were HD at presentation ($P = 0.03$), the degree of DGS ($P = 0.032$), and a low serum albumin at presentation ($P = 0.011$). By Cox regression, the only significant risk factor for ESRD was HD at presentation with a hazard or odds ratio of 5.14 (95% confidence interval, 1.08 to 24.5; $P = 0.04$). There was no correlation between ESRD and the percentage of glomeruli with cellular crescents, glomeruli with necrosis, open glomeruli (without necrosis or crescent formation), or any pathologic parameter other than the degree of DGS.

Discussion

This study details the clinical features, pathologic findings, and outcomes in 23 patients with biopsy-proven PNCNG su-

Table 3. Renal biopsy findings

Pathologic finding	Mean (SD)	Range	Pathologic finding	No. of cases	% of cases
No. of glomeruli	17.9 (9.7)	4–41	Pattern of DGS: nodular/diffuse	7/16	30.4/69.6
% of sclerotic glomeruli	26.9 (15.1)	0–50	Degree of DGS: mild/ moderate/severe	12/9/2	52.2/39.1/8.7
% of glomeruli with cellular crescents	24.9 (18)	0–77	Interstitial inflammation: focal/diffuse ^a	14/9	60.9/39.1
% of glomeruli with fibrous crescents	8.4 (13.2)	0–50	Tubular atrophy and interstitial fibrosis: mild/moderate/ severe ^b	5/11/7	21.7/47.8/30.4
% of glomeruli with necrosis	12.9 (14.6)	0–53	Arteriosclerosis and arteriolar hyalinosis: none/mild/ moderate/severe	1/1/18/3	4.3/4.3/78.3/13
% of open glomeruli without necrosis or crescents	41.6 (20.5)	0–80			

DGS, diabetic glomerulosclerosis; SD, standard deviation.

^aFocal, ≤ 50% of cortical surface area; diffuse, >50%.

^bMild, 0% to 25% of cortical surface area; moderate, 26% to 50%; severe, >50%.

perimposed on DGS. It provides the largest reported experience with the coexistence of these two disease processes. In keeping with the diagnosis of PNCNG, patients were older and presented with ARF and an active urine sediment. Positive ANCA serologies were confirmed in 81.8% of patients.

Only 9 cases of PNCNG and DGS have been reported in the English literature (Table 5) (5–12). These 9 patients share many of same characteristics as the patients in our cohort, including a predominance of patients over the age of 60, P-ANCA seropositivity, presentation with ARF, and poor outcomes despite aggressive immunosuppressive therapy. In particular, 4 of the 9 patients died within 5 mo of biopsy and 2 additional patients remain dialysis-dependent.

Multiple studies have examined the prevalence of nondiabetic renal disease in renal biopsies performed on patients with DM (1,3,14,15). The largest study to date included 393 diabetics from multiple centers in Italy and found that 40% of patients had only DGS, 15% had arterionephrosclerosis and ischemic nephropathy, and 45% had nondiabetic renal disease with or without coexistent DGS (1). The most frequent glomerular diseases found were membranous glomerulopathy, IgA nephropathy, and acute postinfectious glomerulonephritis. Crescentic glomerulonephritis (presumably including all etiologies) was seen in 17 patients (4%) (1); and in 8 of the 17 patients (46%), underlying DGS was identified. A recent study from Hong Kong described the renal biopsy findings in 68 patients with DM and found DGS alone in 35% of patients, nondiabetic renal diseases with DGS in 19%, and nondiabetic renal disease alone in 45% (14). In this study, the most common nondiabetic renal diseases were IgA nephropathy, hypertensive arterionephrosclerosis, and membranous glomerulopathy. No cases of crescentic glomerulonephritis were encountered (14).

Three studies have investigated ANCA serologies in patients

with type I DM who do not have clinical evidence of vasculitis (16–18). In one study from Italy, ANCA was positive in 5 of 22 (23%) patients with longstanding type I DM and negative in all 21 healthy control subjects (16). All 5 seropositive patients had C-ANCA by IIF. ELISA was not performed. In this study, ANCA positivity did not correlate with the degree of proteinuria (16). In a second study from Italy, MPO-ANCA was detected in 34 of 88 (39%) patients with DM but in only 3 of 55 (6%) healthy controls. MPO-ANCA seropositivity did not correlate with age, duration of DM, or HgbA1c levels (17). A more recent study by Schlaffke *et al.* detected ANCA by IIF in 11 of 94 (12%) patients with DM (18). By ELISA, 9 patients had MPO-ANCA and 2 had PR3-ANCA. Similar to the previous studies, ANCA positivity did not correlate with duration of DM, glucose control, diabetic retinopathy, or nephropathy (18). Collectively, these studies suggest a high incidence of ANCA in type I DM, as is the case with multiple autoimmune diseases including systemic lupus erythematosus (19), but the pathogenetic and clinical significance of ANCA in DM remains unclear. The increased prevalence of MPO-ANCA in type I diabetics may be the result of chronic low-grade neutrophil activation (20). Based on our experience and other reports (5–12), most patients with PNCNG superimposed on DGS are older and presumably have type II DM. The prevalence of ANCA in type II DM is not known.

The total number of native kidney biopsies processed in our laboratory during the study period (from 2000 to 2007) was 12,608, including 1336 cases of DGS (10.6%) and 577 cases of PNCNG (4.6%). Based on these numbers, 61 biopsies with PNCNG and coexistent DGS could be predicted to occur by chance, whereas only 23 cases were actually found. These data suggest that the occurrence of both PNCNG and DGS in a single renal biopsy is rare and likely coincidental. However,

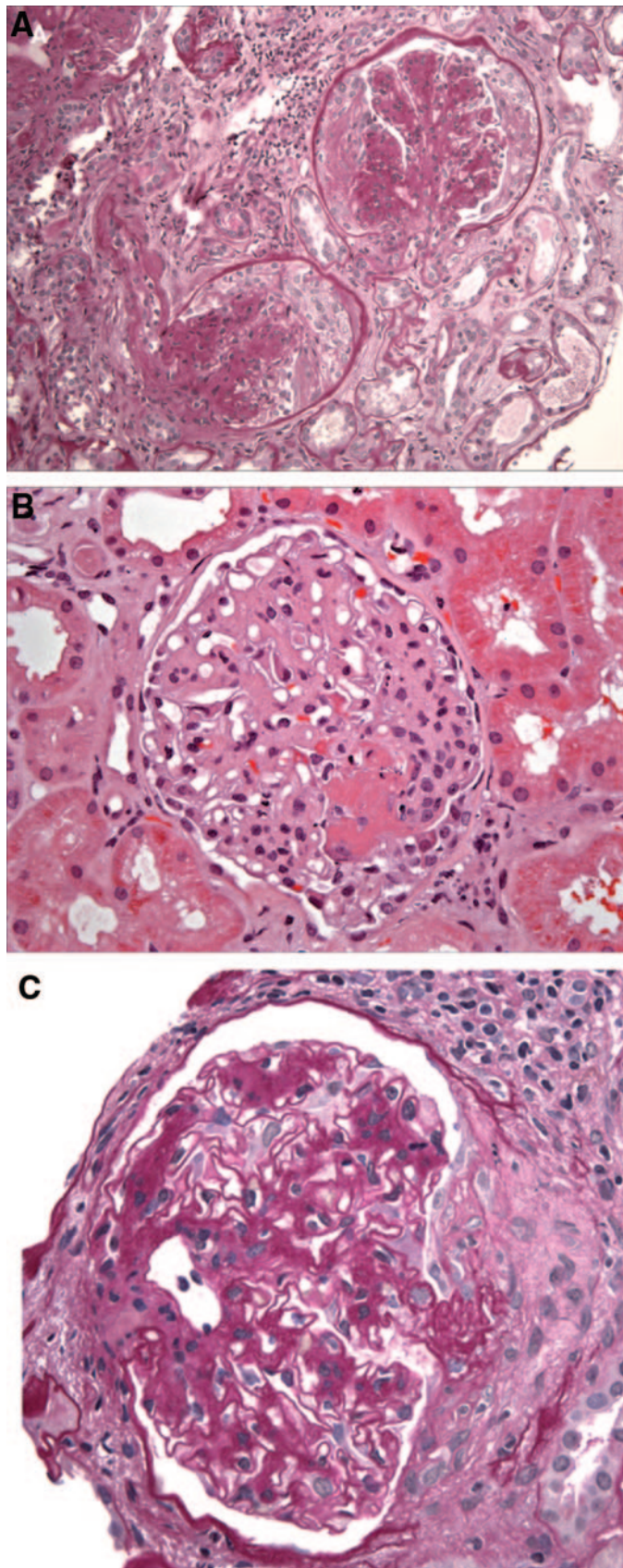


Figure 1. (A) Two glomeruli exhibit nodular diabetic glomerulosclerosis and overlying cellular crescents (periodic acid-Schiff, original magnification $\times 200$). (B) A glomerulus with

Table 4. Clinical follow-up

	No. of patients
Follow-up available	21/23 (91.3%)
Treatment	
steroids	19/21 (90.5%)
cyclophosphamide	14/21 (66.7%)
intravenous	2/21 (9.5%)
oral	12/21 (57.1%)
plasmapheresis	5/21 (23.8%)
Patients on HD at presentation	11/23 (47.8%)
remain on HD	8/11 (72.7%)
transiently discontinued HD	1 (9%)
came off HD	2 (18.2%)
final serum creatinine (mg/dl)	3.25 (3.0–3.5)
duration of follow-up (mo)	7 (4–10)
Patients not on HD at presentation	10/21 (47.6%)
with available follow-up	
became HD-dependent	3/10 (30%)
duration of follow-up until HD (mo), mean (range)	4.5 (1–8)
remain off HD	7/10 (70%)
duration of follow-up (mo)	9.3 (0.25–25)
final serum creatinine (mg/dl)	2.26 (1.4–3.4)
Patient status	
duration of follow-up (mo)	14.6 (0.25–92)
alive	10/21 (47.6%)
alive post-renal transplant	3/21 (14.3%)
died	8/21 (38.1%)
time from biopsy to death (mo)	6.1 (0.25–25)

HD, hemodialysis. Data are mean with range or fraction with corresponding percentage.

because most patients with presumed DGS do not undergo a renal biopsy, the biopsy incidence of DGS does not necessarily reflect its incidence in the general population. Therefore, whether the two processes are coincidental or DGS predisposes to PNCGN cannot be established from our data.

PNCGN is an aggressive condition which, in the absence of immunosuppressive therapy, is associated with 1-yr mortality rate of 80% (21). The prognosis is dramatically improved by immunosuppressive regimens, which commonly include high-dose corticosteroids and CYC. In a recent retrospective, multicenter study of 246 patients from England, the cumulative patient survival at 1 and 5 yr was 82% and 76%, respectively, and 28% of patients developed ESRD (22). In a prospective study of 107 patients with ANCA-associated PNCGN from Chapel Hill, NC who were fol-

diffuse diabetic glomerulosclerosis shows segmental fibrinoid necrosis (hematoxylin and eosin, original magnification $\times 400$). (C) Another glomerulus with diffuse diabetic glomerulosclerosis exhibits a segmental fibrous crescent associated with rupture of Bowman's capsule (periodic acid-Schiff, original magnification $\times 400$).

Table 5. Clinical features of 9 previously reported cases of pauci-immune crescentic glomerulonephritis superimposed on diabetic glomerulosclerosis

Author (reference)	Age (yr)/sex	Duration of diabetes (yr)	Retinopathy	24-h urine protein (g/day)	Creatinine at time of biopsy (mg/dl)	ANCA	Extrarenal manifestations of vasculitis	Treatment	Duration of follow-up (mo)	Outcome
Carstens (5)	40/male	25	Yes	2.7	4 (on HD)	NA	None	PRED/CYC	24	Partial recovery (off HD)
Carstens (5)	61/male	8	Yes	3	3.6	NA	Purpura	PRED/CYC	5	Partial renal recovery/died 5 mo after biopsy
Toth (6)	55/female	2	Yes	5.9	2.2	NA	None	None	0.5	Died 2 wk after biopsy
Maeda (7)	64/female	16	NA	1.3	2.5	P-ANCA	Churg-Strauss syndrome	M-PRED/PRED/PO CYC	12	Stable renal function
Meoro (8)	65/male	13	No	NA	5.2 (HD)	P-ANCA/MPO-ANCA	None	M-PRED/PRED/PO CYC	1	Remained on HD
Ninomiya (9)	78/male	30	Yes	4	12.8 (HD)	P-ANCA/MPO-ANCA	Pulmonary fibrosis	M-PRED/PRED	2	Remained on HD
Lui (10)	72/female	10	Yes	5.4	4.1	P-ANCA/MPO-ANCA	None	M-PRED/PRED/PO CYC	8	Partial renal recovery
Hill (11)	56/male	10	Yes	8	3.9	P-ANCA/MPO-ANCA	None	M-PRED/PRED/PO CYC	2	HD/died 2 mo after biopsy
Nishijima (12)	88/male	30	No	7.2	7.2 (HD)	MPO-ANCA	None	M-PRED	2.5	Remained on HD/died 2.5 mo after biopsy

CYC, cyclophosphamide; HD, hemodialysis; M-PRED, methylprednisolone; NA, not available; PO, oral; PRED, prednisone.

lowed for a mean of 2.5 yr, 11% had disease-related deaths and 43% progressed to ESRD (23). In another study from Slovenia of 37 elderly patients with ANCA-associated PNCNGN followed for a mean of 32 mo, 16% developed ESRD. The actuarial renal survival was 92% at 1 yr and 76% at 3 yr (24).

The prognosis for renal and patient survival is considerably worse for PNCNGN in patients with underlying DGS. Considering all 30 patients with available follow-up from our study and the previously reported cases (5–12), 12 patients (40%) died within 1 wk to 25 mo (mean, 5 mo) of biopsy and 10 of the remaining 18 patients (55.6%) became dialysis-dependent within 0 to 13 mo (mean, 1.7 mo). None of the patients in our cohort had a return to baseline serum creatinine level. DGS likely compromises the kidney's ability to recover from superimposed PNCNGN. The poor patient survival is undoubtedly multifactorial, relating to systemic vasculitis, DM, immunosuppressive therapy given to patients with impaired immunity and increased susceptibility to infection, and other comorbidities that commonly accompany longstanding DM.

Correlates of ESRD were HD and low serum albumin at presentation and the degree of DGS. Low serum albumin may reflect the underlying severity of DGS and proteinuria. There was no correlation between ESRD and the percentage of glomeruli with cellular crescents or necrosis. This is likely the result of the small sample size and the fact that patients with a higher percentage of glomeruli with cellular crescents ($P = 0.003$) or necrosis (0.031) were more likely to have received CYC.

PNCNGN should be considered in the differential diagnosis for all patients with ARF and an active urine sediment, including individuals with DM. In this setting, ANCA serologies should be widely used. From the pathologic perspective, establishing the diagnosis of DGS with superimposed PNCNGN is not particularly difficult. Biopsies with DGS may exhibit subcapsular fibrosis with crescent-like proliferations that may resemble

fibrous crescents or may have intracapillary fibrin within diabetic glomerular microaneurysms. Both of these findings must be distinguished from PNCNGN. A helpful clue is that GBM rupture should only be seen in PNCNGN. Another potential pitfall is to misinterpret the linear staining of GBMs for IgG that is commonly encountered in DGS as representing evidence of anti-GBM disease. This may be avoided by recognizing that staining for IgG in DGS is typically of low intensity and is accompanied by similar or greater intensity linear staining of GBMs for albumin. When necessary, anti-GBM testing may be performed.

Recent increases in the prevalence of DM will undoubtedly lead to an increase in the number of renal biopsies performed on diabetic patients. In patients with DM, renal biopsy may reveal DGS, nondiabetic renal disease, or both processes. We report the largest experience to date of ANCA-associated PNCNGN superimposed on DGS. This condition is most common in elderly patients with longstanding DM who present with ARF and active urine sediment. The management of patients with this dual glomerulopathy is extremely challenging, and the prognosis is dismal with poor renal and patient outcomes.

Disclosures

None.

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