Postinfectious Glomerulonephritis in the Elderly

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ABSTRACT

Postinfectious glomerulonephritis (PIGN) is primarily a childhood disease that occurs after an upper respiratory tract infection or impetigo; its occurrence in older patients is not well characterized. Here, we report 109 cases of PIGN in patients ≥65 years old diagnosed by renal biopsy. The male to female ratio was 2.8:1. An immunocompromised background was present in 61%, most commonly diabetes or malignancy. The most common site of infection was skin, followed by pneumonia and urinary tract infection. The most common causative agent was staphylococcus (46%) followed by streptococcus (16%) and unusual gram-negative organisms. Hypocomplementemia was present in 72%. The mean peak serum creatinine was 5.1 mg/dl, and 46% of patients required acute dialysis. The most common light microscopic patterns were diffuse (53%), focal (28%), and mesangial (13%) proliferative glomerulonephritis. IgA-dominant PIGN occurred in 17%. Of the 72 patients with ≥3 months of follow-up (mean, 29 months), 22% achieved complete recovery, 44% had persistent renal dysfunction, and 33% progressed to ESRD. The presence of diabetes, higher creatinine at biopsy, dialysis at presentation, the presence of diabetic glomerulosclerosis, and greater tubular atrophy and interstitial fibrosis predicted ESRD. In summary, the epidemiology of PIGN is shifting as the population ages. Older men and patients with diabetes or malignancy are particularly at risk, and the sites of infection and causative organisms differ from the typical childhood disease. Prognosis for these older patients is poor, with fewer than 25% recovering full renal function.

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The proportion of the elderly population in the Western world is growing. In 2000, 12% of the U.S. population was age 65 or older, and this percentage is expected to increase to 16% in 2020 and to 20% in 2030.[1] Renal disease is more prevalent in the elderly. According to the U.S. National Health and Nutrition Examination Surveys data, the prevalence of chronic kidney disease among noninstitutionalized individuals ≥70 years old has increased from 38% in the period 1988 to 1994 to 47% in the period 1999 to 2004.[2] Many factors likely contribute, including the longer life expectancy and progressive decline in GFR with age, exposure to nephrotoxins, and the high rates of comorbid conditions, including diabetes, hypertension, hyperlipidemia, cardiovascular disease, and neoplasia.[3] The health risks associated with chronic kidney disease, including cardiovascular disease and the complications of dialysis and transplantation, with their attendant socio-economic burden, underscore the importance of early recognition and treatment. The biology of aging and such concurrent conditions as hypertension and diabetes frequently modify the clinical presentation, pathology, and natural history of renal diseases in the elderly; therefore, clinicopatho-

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logic studies are needed to specifically address kidney disease in this rapidly growing segment of the population.

Renal diseases with a higher incidence in the elderly include contrast nephropathy, hypertensive nephrosclerosis, pauci-immune crescentic glomerulonephritis (GN), ischemic nephropathy, cholesterol embolization, and myeloma cast nephropathy.[4,5] Among elderly patients with acute renal insufficiency coming to renal biopsy, the most common finding is pauci-immune crescentic GN (31 to 71%), followed by acute interstitial nephritis (7 to 19%).[4–6] Postinfectious glomerulonephritis (PIGN) is less frequent, encountered in 3 to 6% of biopsies, and is frequently unexpected clinically.[4,5]

PIGN is primarily a childhood disease that occurs after upper respiratory tract infection or impetigo.[7,8] Streptococcus is the most common responsible bacterium for PIGN in both children and adults.[7–12] In adults, PIGN is more common in immunocompromised patients, particularly diabetics and alcoholics. The incidence of PIGN in the developed countries has declined over the past several decades.[8,12,13]

Aging has emerged as an important risk factor for adult PIGN. Four decades ago, only 4 to 6% of reported adults with PIGN were ≥65 years compared with 34% in recent reports.[9,14,15] In the Italian Registry of Renal Biopsy, the incidence of PIGN in the elderly (after the age of 60) is 0.9 patients/million compared with 0.4 patients/million in younger adults.[16] This is likely the result of prolonged life expectancy, higher frequency and severity of infections in the elderly,[17] and increased prevalence of underlying conditions that predispose to infection, particularly diabetes and cancer. There have been no prior studies specifically addressing the clinicopathologic characteristics of PIGN in the elderly. This study reports the demographics, clinical features, pathologic findings, and outcome data on 109 elderly patients (≥65 years of age) with PIGN diagnosed at two major U.S. renal biopsy centers.

RESULTS

Clinical Features

Most patients were Caucasian (75%) and male (73%) (Table 1). Eighteen percent of patients were very elderly (≥80 years of age). Sixty-one percent of patients had immunocompromised background, and the most frequent predisposing factor for infection was diabetes, which was present in nearly half of patients (Table 1). Fifteen patients (14%) had an underlying malignancy, including four with colon carcinoma, four with prostate carcinoma, three with lung carcinoma, one with breast carcinoma, one with chronic myelocytic leukemia, one with lymphoma, and one with multiple myeloma. The site of infection was identified in 83% of patients, the most common sites being skin (28%) in both diabetics and nondiabetics, followed by lung (pneumonia) (16%) and urinary tract (13%) (Table 2). The skin infections included cellulitis (primarily of the lower extremities) in 22 patients, surgical wound infections in four patients, skin abscesses of the lower extremity in two patients, IV line infection in one patient, stump infection after amputation below the knee in one patient, and infection of a lower extremity gortex graft in one patient. Ten percent of patients had two coexistent sites of infection (Table 2). The infectious agent was identified in 66% of patients (by positive culture in the case of nonstreptococcal infection and by positive culture, elevated anti-streptolysin O antibody, or anti-DNase B antibody in the case of streptococcal infection) (Table 3). Staphylococcus was by far the most common causative agent, found in 46% of patients, and was almost three times more common than streptococcus (Table 3). Of the 50 patients with staphy-

Table 1. Demographics and predisposing factors to infection (109 patients)

	No. of Patients (%)
Male/female	80/29 (73/27)
Age in years	
65 to 69	37 (34)
70 to 79	52 (48)
≥80	20 (18)
Race	
white	82 (75)
hispanic	7 (6)
African American	5 (5)
Native American	3 (3)
Asian	2 (2)
undisclosed	10 (9)
Predisposing factors for infection	67 (61)
DM	53 (49)
malignancies	15 (14) (six had DM)
alcoholism	4 (4) (three had DM)
severe malnutrition	1 (1)
myelofibrosis	1 (1)
cirrhosis	1 (1)
synthetic heart valve	1 (1)

DM, diabetes mellitus.

Table 2. Site of infection (109 patients)

Site of Infection[a]	No. of Patients (%)
Skin	31 (28)
Lung	17 (16)
Urinary tract	14 (13)
Upper respiratory tract	11 (10)
Osteomyelitis	8 (7)
Endocarditis	7 (6)
Deep-seated abscess	5 (5)
Empyema	2 (2)
Prostatitis	1 (1)
Infected pancreatic cyst	1 (1)
Phlebitis	1 (1)
Sepsis (source not identified)	3 (3)
No clinical evidence of infection	19 (17)

[a]11 patients had two sites of infection, including skin and pneumonia in one, skin and urinary tract in one, skin and osteomyelitis in two, skin and endocarditis in one, skin and deep-seated abscess in one, upper respiratory tract and urinary tract in two, urinary tract and osteomyelitis in one, deep-seated abscess and osteomyelitis in one, and pneumonia and empyema in one.

Table 3. Infectious agents (109 patients)

Infectious Agent[a]	No. of Patients (%)
Staphylococcus	50 (46)
Streptococcus[b]	17 (16)
E. coli	5 (5)
Pseudomonas	2 (2)
Actinetobacter	1 (1)
Serratia marcescens	1 (1)
Proteus	1 (1)
Klebsiella	1 (1)
Enterobacter cloacae	1 (1)
Candida	1 (1)
Unknown	37 (34)

[a]In seven patients, cultures grew two or three bacteria (staphylococcus and *E. coli* in three; staphylococcus and enterococcus in one; staphylococcus and *S. marcescens* in one; *E. coli* and enterococcus in one; and staphylococcus, proteus, and pseudomonas in one).
[b]Including five patients with infection by enterococci (group D streptococci).

Table 4. Clinical characteristics at presentation

	No. of Patients (%)
New onset hypertension	13 (12)
Long-standing hypertension	78 (72)
Peripheral edema	72/106 (68)
New onset congestive heart failure	28/106 (26)
Proteinuria <1 g/24 h	19/72 (26)
Proteinuria 1 to 3 g/24 h	22/72 (31)
Proteinuria >3 g/24 h	31/72 (43)
Full nephrotic syndrome	23/87 (26)
Hypoalbuminemia	83/91 (91)
Hematuria	
microscopic or macroscopic	98/103 (95)
macroscopic hematuria	19 (17)
Leukocyturia	63/97 (65)
Creatinine ≤1.2 mg/dl	4/108 (4)
Creatinine 1.21 to 2.0 mg/dl	14/108 (13)
Creatinine >2.0 mg/dl	90/108 (83)
Dialysis at biopsy	48/105 (46)
Low C3	57/83 (69)
Low C4	29/83 (35)
Low C3 or C4	60/83 (72)
Low C3 and C4	26/83 (31)

lococcal infection, only five had coagulase-negative staphylococcus including two patients with *Staphylococcus epidermidis*, one with *Staphylococcus hemolyticus*, and two with unknown coagulase-negative staphylococcus species. The remaining 45 patients had *Staphylococcus aureus* including 23 with methicillin-resistant *S. aureus*, 16 with methicillin-sensitive *S. aureus*, and six in whom the *S. aureus* antibiotic sensitivity test results were not available. Skin was the most frequent site of staphylococcal infection (38%), whereas the upper respiratory tract was the most common site for streptococcal infection (29%). The mean time from clinical onset of infection to renal disease was 2 weeks (range, 0 to 16 weeks). In 45% of patients, the onset of clinical renal disease coincided with the first clinical recognition of infection. The time from clinically apparent onset of renal disease to biopsy was ≤4 weeks in 79 of 93 patients (85%) with available data.

At presentation, 72% of patients had longstanding hypertension, and 12% had new onset hypertension (Table 4). Peripheral edema was present in two-thirds of patients. The mean 24-hour urine protein was 3.6 g. Forty-three percent of patients had nephrotic range proteinuria (NRP), and nephrotic syndrome was present in 26% of patients. Ninety-one percent of the 91 patients with available data had hypoalbuminemia. Mean serum albumin at biopsy was 2.7 g/dl. Hematuria was present in 95% of patients, including macroscopic hematuria in 17%. Leukocyturia was present in 65% of patients (Table 4).

The mean peak serum creatinine was 5.1 mg/dl, whereas the mean serum creatinine at biopsy was 4.5 mg/dl (Table 4). Only two patients (2%) had a peak serum creatinine in the normal range, both of whom had resolving PIGN on biopsy (one with mesangial proliferative GN and one with focal endocapillary proliferative GN) without underlying diabetic glomerulosclerosis (DGS). Eighty-three percent of patients had a serum creatinine >2 mg/dl at biopsy, and 67% had a peak serum creatinine >4.0 mg/dl. Forty-six percent of patients required dialysis at biopsy for uremic symptoms and/or fluid overload. In 26% of patients, the nephrologist described the new clinical development of congestive heart failure at presentation, although measures of cardiac function were not available. Correlates of higher serum creatinine at biopsy were the presence of nephrotic syndrome ($P < 0.001$), DGS ($P = 0.044$), and global (*versus* segmental) subendothelial deposits ($P = 0.037$). Baseline serum creatinine, available in 72 patients, was elevated in 33% of patients. Mean baseline serum creatinine was 1.32 mg/dl (range, 0.7 to 4.2). Testing for serum complement (C) was performed in 83 patients, of which 69% had depressed C3, and 35% had depressed C4. Among the 83 patients tested, 31% had depression of both C3 and C4, whereas 72% had a depression of either C3 or C4 (Table 4). Anti-neutrophil cytoplasm autoantibody (ANCA) was positive in five of 66 patients (8%) with available data. Testing for serum cryoglobulin was performed in 16 patients, all of whom had negative titers.

Pathologic Findings on Light Microscopy

The most common histologic pattern of glomerular injury on light microscopy (LM) was diffuse endocapillary proliferative and exudative GN (Figures 1 and 2), found in 53% of patients, followed by focal endocapillary proliferative and exudative GN (28% of patients) and mesangial proliferative GN (13%). Only one patient who had staphylococcal skin infection had a membranoproliferative GN pattern. Diffuse crescentic and necrotizing GN (defined by crescents or necrosis involving ≥50% of glomeruli) was seen in five patients (5%), of which four also had focal endocapillary hypercellularity and one had diffuse endocapillary hypercellularity. Two of these five patients had positive ANCA. The causative agent, identified in three of these five patients, was staphylococcus.

The mean glomerular count and percentage of sclerotic glo-

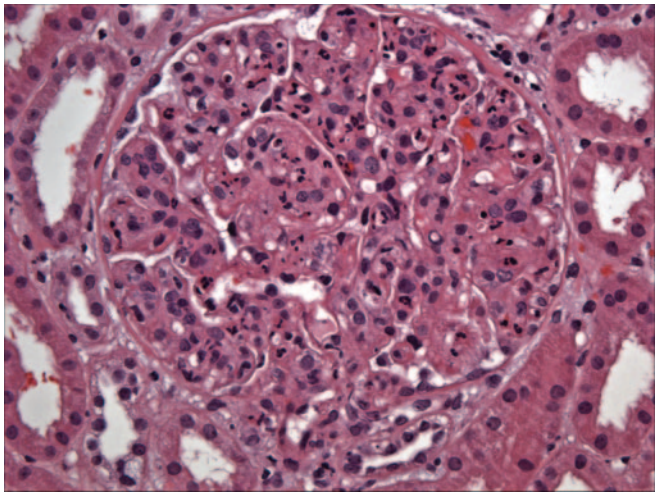

Figure 1. The glomerular capillaries are globally occluded by numerous infiltrating neutrophils, as well as proliferation of glomerular endothelial and mesangial cells (hematoxylin and eosin, ×400).

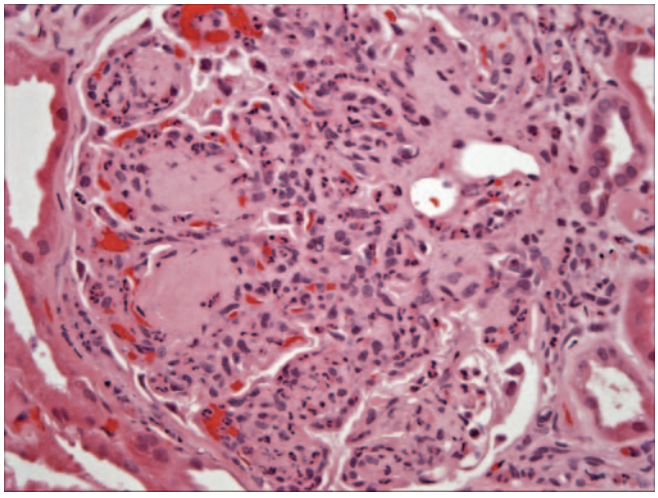

Figure 2. The glomerulus exhibits segmental nodular mesangial sclerosis, consistent with underlying diabetic glomerulosclerosis. The glomerular capillary lumina are occluded by the superimposed severe endocapillary proliferation including numerous infiltrating neutrophils (hematoxylin and eosin, ×400).

meruli were 17 and 22% (Table 5). Glomerular neutrophil infiltration was seen in 81% of patients. Cellular crescents were present in 37% of patients but affected ≥20% of glomeruli in only 13% of patients. Segmental glomerular necrosis was encountered in 19% of patients. Forty-three patients (39%) had underlying DGS. In these patients, the DGS class according to the recently published Renal Pathology Society classification was I in 16% of patients, II in 44% patients, III in 26% of patients, and IV in 14% of patients.[18] Interstitial inflammation with a mixed infiltrate of lymphocytes, monocytes, plasma cells, and neutrophils was present in 95% of patients and was focal in most cases. In 11% of patients the interstitial neutrophils were numerous, and 5% of patients had neutrophil casts. Secondary acute tubular injury, interstitial edema, and red blood cell casts were seen in 88, 54, and 47% of patients, respectively. The degree of tubular atrophy and interstitial fibrosis was mild in most patients (Table 5). Moderate or severe tubular atrophy and interstitial fibrosis were more common in patients with underlying DGS (37% *versus* 14%, $P = 0.006$). Similarly, moderate or severe arteriosclerosis and arteriolar hyalinosis were more common in patients with underlying DGS (79% *versus* 58%, $P = 0.024$). Focal septic arteritis was identified in one patient (1%).

Immunofluorescence Findings

Glomeruli were sampled for immunofluorescence (IF) in 97 patients (89%). The most common staining pattern on IF, seen in 69% of the 97 patients in which glomeruli where sampled was granular mesangial and glomerular capillary wall, resembling the "starry sky pattern" described by Sorger *et al.*[19] (Figure 3). In 8% of patients, the staining was predominantly glomerular capillary wall resembling the "garland pattern."[19] In the remaining 23% of patients, the staining was predominantly mesangial ("mesangial pattern").[19] C3 was the dominant or codominant immune reactant detected in glomeruli in all patients (100%), with a mean staining intensity (MSI) of 2.5+ (on a scale of 0.5 to 3+). In 26 patients (27%), there was sole glomerular positivity for C3. In the remaining patients, there was concomitant glomerular granular positivity for one or more additional immune reactants, including IgG (40% of patients, MSI when positive 1.3+), IgA (39% of patients, MSI 1.3+), IgM (35% of patients, MSI 0.7+), C1q (23% of patients, MSI 1.0+), kappa (41% of patients, MSI 1.2+), and lambda (41% of patients, MSI 1.3+). There was no correlation between sole glomerular staining for C3 on IF and the LM pattern ($P = 0.312$) or a preferential location of subepithelial deposits at the mesangial waist ($P = 0.779$). In 16 patients (17%), including 11 diabetics, IgA was the dominant Ig deposited in glomeruli (intensity, ≥1+); the causative infectious agent was staphylococcus in nine, enterobacter cloacae in one, *Escherichia coli* and enterococcus in one, and unknown in five.

Electron Microscopy (EM) Findings

EM was performed on all biopsies. Subepithelial electron dense deposits were present in 92% of patients and exhibited a "hump-shaped" appearance in most cases (Figure 4). In cases of resolving PIGN, the subepithelial deposits were preferentially located at the glomerular basement membrane reflection over the mesangium. Subendothelial deposits were seen in 66% of patients and were small and rare in the majority of patients. Mesangial deposits were detected in 87% of patients and were global in 33% of patients. None of the patients exhibited organized deposits. Patients with underlying DGS displayed variable degrees of mesangial sclerosis and thickening of the glomerular and tubular basement membranes. The mean degree of foot process effacement was <25% in 22 patients, 25 to 50% in 52 patients, and >50% in 35 patients.

Table 5. Light microscopic findings

Pathologic Findings	No. of Patients	Percentage of Patients
Mean number of glomeruli	17	
Percentage of globally sclerotic glomeruli	22%	
Number of cases with cellular crescents (<20% of glomeruli, ≥20% of glomeruli)	40 (26/14)	37 (65/35)
Number of cases with necrosis (<20% of glomeruli, ≥20% of glomeruli)	21 (17, 4)	19 (81, 19)
Interstitial inflammation: none/focal/diffuse	5/93/11	5/85/10
Acute tubular injury: none/focal/diffuse	13/54/42	12/50/39
Tubular atrophy and interstitial fibrosis: none/mild/moderate/severe	13/71/21/4	12/65/19/4
Arteriosclerosis and arteriolar hyalinosis: none/mild/moderate/severe	3/34/64/8	3/31/59/7

Outcome

Clinical follow-up was available in 98 patients (90%). The duration of follow-up was <3 months in 26 patients (27%) and ≥3 months in 72 patients (73%). Of the 26 patients with <3 months of follow-up, 15 remained dialysis-dependent, and 11 had persistent renal dysfunction (PRD). Fourteen of these 26 patients died. The mean duration of follow-up for the 72 patients with ≥3 months follow-up was 29 months (range, 3 to 112 months). Of these patients, 16 (22%) achieved complete recovery (CR), 32 (44%) had PRD, and 24 (33%) progressed to ESRD (Table 6). Among the 24 patients who progressed to ESRD, 16 had required dialysis at the time of biopsy and never recovered renal function, and eight started permanent dialysis 2 to 44 months postbiopsy. Nine of the 72 patients died, including five with ESRD and four with PRD. Thirty-two of the 72 patients with ≥3 months of follow-up were on dialysis at the time of biopsy. Of these, 16 remained on dialysis, and 16 came off dialysis 0.5 to 10 months postbiopsy (mean, 2.5 months). The final outcome in the 16 patients who came off dialysis was CR in five, PRD in 10, and resumption of dialysis in one.

Univariate analysis was performed on all 98 patients with follow-up. By the Kaplan-Meier survival estimates, the correlates of reaching ESRD were the presence of diabetes, dialysis at presentation, presence of DGS, and greater degree of tubular atrophy and interstitial fibrosis (Table 7). By the Cox proportional hazards model (Cox regression), predictors of reaching ESRD were serum creatinine at biopsy (hazard ratio [HR], 1.314; 95% confidence interval [CI], 1.166 to 1.481; $P < 0.001$), serum albumin (HR, 0.503; 95% CI, 0.291 to 0.869; $P = 0.014$), and the tubular atrophy and interstitial fibrosis score (HR, 1.845; 95% CI, 1.184 to 2.876; $P = 0.007$). There were no significant correlates on univariate analysis between renal outcome and age, gender, degree of proteinuria, serum complement, site of infection, or infectious organism.

Multivariate analysis using binary logistic regression was performed only on the 72 patients with ≥3 months of follow-up. Correlates of reaching ESRD by multivariate analysis were a higher serum creatinine at biopsy (HR, 1.296; 95% CI, 1.142 to 1.471; $P < 0.001$) and a greater degree of tubular atrophy and interstitial fibrosis (HR, 1.735; 95% CI, 1.045 to 2.882; $P = 0.033$).

Patients with known infection were treated with antibiotics. Twenty-two of the 98 patients with available outcome data were treated with steroids for variable periods of time. The indication for steroid therapy was renal insufficiency with or without crescents. Of these patients, three had CR, 12 had PRD, seven progressed to ESRD, and four died. No correlation was found between steroid therapy and renal outcome.

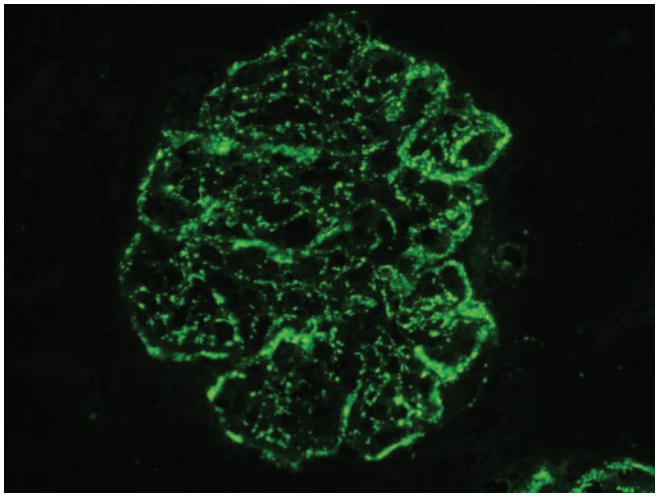

Figure 3. An immunofluorescence image shows coarsely granular positivity in a global glomerular capillary wall and mesangial distribution (anti-C3, ×400).

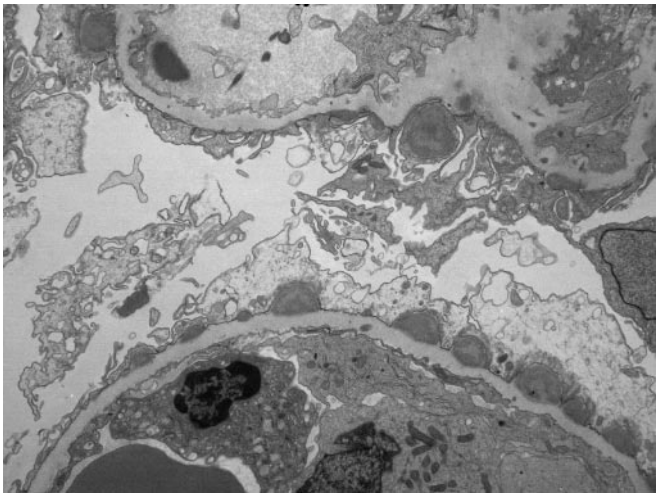

Figure 4. This glomerulus exhibits multiple hump-shaped subepithelial deposits involving the peripheral glomerular capillary walls and mesangial waist, without intervening glomerular basement membrane spikes. There is localized effacement of foot processes overlying the humps (EM, ×5800).

Table 6. Outcome in 72 patients with ≥3 months of follow-up

	All Patients ($n = 72$)	Patients without DGS ($n = 43$)	Patients with DGS ($n = 29$)	*P*
Mean duration of follow-up (range) in months	29 (3 to 112)	29 (3 to 112)	31 (3 to 104)	0.77
Complete recovery	16 (22%)	10 (23%)	6 (21%)	1.00
Persistent renal dysfunction (PRD)	32 (44%)	25 (58%)	7 (24%)	0.007
End stage renal disease	24 (33%)	8 (19%)	16 (55%)	0.002
Death	9 (13%)	7 (16%)	2 (7%)	0.30

For the overall analysis of outcome (three groups: CR, PRD, and ESRD) *versus* the presence of DGS, $P = 0.02$ by the Kruskal-Wallis test.

DISCUSSION

Table 8 compares the major characteristics of PIGN in the 109 elderly patients in this report with those of 57 adults aged 16 to 64 years that we previously reported.[9] Similar to other age groups, elderly PIGN appears to be more common in men.[9,14,20] In this study, close to three-fourths of our elderly patients with PIGN were men. This is despite the fact that women have longer life expectancy, with the female to male ratio of the U.S. population aged ≥65 years being 1.4:1.[1] The reason for this gender difference is unknown. Elderly patients with PIGN are more likely than children and adults to be immunocompromised. Sixty-one percent of our elderly patients had an immunocompromised background compared with 32% of our adult patients ($P < 0.001$). Diabetes was by far the most prevalent underlying condition predisposing to infection, seen in almost half of the patients. Malignancy, particularly carcinoma, was the second most common predisposing condition but at a much lower incidence (14%) (Table 8). These two conditions likely contribute to the higher incidence of PIGN in elderly *versus* younger adults.

The sites of infection and the causative bacteria in the elderly with PIGN are also different from those in children and adults. The majority of cases in children and adults are caused by a streptococcal upper respiratory tract or skin infection (Table 8).[9–11,14] In contrast, we found that in the elderly, skin infection, pneumonia, and urinary tract infection are more common than upper respiratory tract infection. In the elderly, staphylococcal infection is almost three times more common than streptococcal infection, followed by many unusual gram negative organisms (Table 8). The latent period between infection and onset of renal disease in children with PIGN is typically 1 to 6 weeks. In contrast, in nearly half of elderly patients in this report, the infection was first discovered at the onset of renal disease, indicating that infection may go unrecognized for some time. Signs of infection in the elderly population are often nonspecific, and fever, the cardinal sign of infection in younger adults, is absent in 20 to 30% of patients, frequently leading to a delay in diagnosis.[21]

Age-related diseases such as hypertension, coronary artery disease, and diabetes alter the clinical picture of PIGN in elderly patients. New onset or exacerbated congestive heart failure is more common in the elderly, because of the increased prevalence of underlying cardiovascular disease and reduced ability to handle the salt and water retention associated with acute nephritis.[22] Elderly patients have a higher rate of more severe acute renal insufficiency at presentation. The mean peak serum creatinine in our study was 5.1 mg/dl in the elderly group compared with 3.8 mg/dl in the adult group ($P = 0.029$) (Table 8). The percentage of elderly patients in our study with a peak serum creatinine >4.0 mg/dl was 67% compared with 32% in our younger

Table 7. Predictors of progression to ESRD by Kaplan-Meier survival estimates (univariate analysis)

Factor	Mean Time from Biopsy to ESRD in months	95% CI	*P*
Diabetes			
yes	40.06	25.08 to 59.18	0.0152
no	77.53	60.50 to 94.56	
Diabetic glomerulosclerosis			
yes	34.40	17.82 to 50.99	0.0014
no	79.45	64.39 to 94.52	
Dialysis at biopsy			
yes	34.48	19.38 to 49.59	<0.001
no	90.94	74.43 to 107.45	
Tubular atrophy and intersitial fibrosis			
none	56.96	35.38 to 78.55	0.0131
mild	67.94	51.34 to 84.53	
moderate	27.58	10.45 to 44.71	
marked	8.00	0.00 to 23.68	
Glomerular pattern on light microscopy			
MesPGN	71.37	44.80 to 97.94	0.0575
F/DPGN or MPGN	60.56	45.81 to 75.31	
crescentic GN	7.67	0.00 to 22.69	
Glomerular pattern on immunofluorescence			
mesangial	45.74	22.39 to 69.10	0.3941
garland	41.33	17.86 to 64.80	
starry sky	68.51	47.76 to 89.26	

MesPGN, mesangial proliferative glomerulonephritis; F/DPGN, focal or diffuse proliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis.

Table 8. Comparison of the clinical characteristics of PIGN in elderly patients *versus* adult patients

	Elderly patients (≥65 years)	Adult patients (16 to 64 years)[a]	*P*
No. of patients	109	57	
Male/female	2.8/1	1.4/1	0.054
Immunocompromised background	67 (61%)	18 (32%)	<0.001
diabetes mellitus	53 (49%)	13 (23%)	0.0014
malignancies	15 (14%)	1 (2%)	0.012
alcoholism	4 (4%)	3 (5%)	0.69 (NS)
Most common site of infection			
skin	31 (28%)	6 (11%)	0.01
pneumonia	17 (16%)	9 (16%)	1.00 (NS)
urinary tract	14 (13%)	2 (4%)	0.058
upper respiratory tract	11 (10%)	18 (32%)	0.001
Most common bacteria			
staphylococcus	50 (46%)	8 (14%)	<0.001
streptococcus	17 (16%)	19 (33%)	0.011
Mean 24-hour urine protein at presentation	3.6 g	3.8 g	0.545 (NS)
Mean peak serum creatinine	5.1 mg/dl	3.8 mg/dl	<0.001
Peak serum creatinine >4 mg/dl	71/108 (67%)	18 (32%)	<0.001
IgA-dominant staining on immunofluorescence	16/97(17%)	3/57 (5%)	0.045
Renal outcome (in patients with ≥3 months of follow-up)			0.075[b]
complete recovery	16/72 (22%)	14/32 (44%)	0.035
persistent renal dysfunction	32/72 (44%)	10/32 (31%)	0.28 (NS)
end-stage renal disease	24/72 (33%)	8/32 (25%)	0.49 (NS)
Mortality rate (any time after biopsy)	23/98 (23%)	5/44 (11%)	0.11 (NS)
Early mortality rate (death within 2 months post-biopsy)	15/98 (15%)	3/44 (7%)	0.19 (NS)

[a]Adult comparison group previously reported in reference 9.
[b]By the Kruskal-Wallis test for the comparison of outcome (CR/PRD/ESRD) *versus* age group.

adult patients and 27% in the classic 1974 study by Baldwin *et al.*,[14] which reported 126 PIGN patients including 37 children, 84 adults, and 5 elderly individuals.

The vast majority of children with PIGN recover completely.[23–25] Adults have a less favorable prognosis. Large studies performed before 1980 of adult PIGN in which only a small minority of patients were ≥65 reported that CR can be achieved in 53 to 76% of patients.[12,26,27] A more recent study from Italy of 50 patients aged 29 to 65 years found a CR rate of 43%.[10] On the basis of the results from this large study, it appears that PIGN in elderly patients has a worse prognosis than in younger adults and children. CR occurred in only 22% of the elderly group compared with 44% of the adult group ($P = 0.035$) (Table 8). Not surprisingly, we found that the presence of diabetes and the findings of DGS were associated with worse prognosis in the elderly patients by univariate analysis. Other poor prognostic factors in our study were higher creatinine at biopsy, low serum albumin, and greater tubular atrophy and interstitial fibrosis.

PIGN should be considered in the differential diagnosis for elderly patients with severe acute renal failure and active urine sediment. In this setting, pauci-immune crescentic GN is far more common,[4–6,28] and therefore testing for ANCA is recommended. ANCA seropositivity, however, requires tissue confirmation for definitive diagnosis of pauci-immune crescentic GN. In our study, five patients (two with staphylococcal pneumonia, one with streptococcal urinary tract infection, and two with no identifiable infection) had ANCA seropositivity at presentation (two with perinuclear ANCA, one with myeloperoxidase [MPO]-ANCA, one with proteinase 3 [PR3]-ANCA, and one with an unknown pattern). On biopsy, three patients had no crescents. The remaining two patients showed diffuse crescentic and focal endocapillary proliferative GN with C3-dominant staining on IF and hump-shaped subepithelial deposits on EM. In these two patients, ANCA seropositivity (PR3-ANCA in one and perinuclear ANCA in one) may have contributed to the development of a crescentic phenotype in a subacute phase of PIGN. Cytoplasmic ANCA seropositivity has been reported in patients with endocarditis-associated crescentic infectious GN, particularly due to streptococcus.[9,29] ANCA-associated crescentic GN may also occur superimposed on other types of immune-complex GN, including membranous glomerulonephritis,[30] IgA nephropathy,[31] and lupus nephritis[32], suggesting a synergistic effect.

IgA-dominant PIGN is a newly recognized form of PIGN.[33–36] It typically occurs in patients with staphylococcal infection, especially those with underlying DGS. In our study, 16% of patients in the elderly patients group showed this pattern on IF compared with only 5% in the younger age group ($P = 0.045$). Therefore, this pattern appears to be more common in the elderly patients, likely because of the higher incidence of staphylococcal infection and diabetes. It is unlikely that IgA-dominant PIGN represents an exacerbation of pre-existing primary IgA nephropathy, because none of our patients had any history of prior glomerulonephritis. Of note, of the 11 patients in our study with this pattern in whom the causative bacterium was known, nine had staphylococcal infection, one had enterobacter cloacae, and one had both *E. coli* and enterococcus. Therefore, this form can rarely be seen in association with nonstaphylococcal infections.

In summary, the epidemiology of PIGN is evolving as the population ages. Elderly men, diabetics and patients with malignancy are particularly at risk. Contrary to children and younger adults, skin infections, pneumonia, and urinary tract

infections are more common than upper respiratory tract infection, and staphylococcal infection is almost three times more common than streptococcal infection. In close to half of patients, the first recognition of infection coincides with the onset of signs and symptoms of glomerulonephritis, suggesting that many infections are subclinical. Elderly patients have a higher rate of more severe acute renal insufficiency, which necessitates dialysis in close to half. The prognosis of PIGN in the elderly is worse than in children and young adults, with less than a quarter of patients fully recovering renal function. Greater awareness of the atypical presentation and course of PIGN in the elderly is needed to ensure prompt diagnosis.

CONCISE METHODS

Ninety-three elderly patients (≥65 years of age) with a diagnosis of PIGN were identified by retrospective review of all native renal biopsies received and processed at the Mayo Clinic (Rochester, Minnesota) from 2000 to 2010. During the study period, the total number of native kidney biopsies from patients of all ages was 47,357, and that from elderly patients (≥65 years of age) was 10,080. This indicates that the biopsy incidence of PIGN in the elderly population is 0.9%. The diagnosis of PIGN was established by clinicopathologic correlation. For the purpose of this study, at least three of the following five criteria were required for study entry: (*1*) clinical or laboratory evidence of infection preceding the onset of GN; (*2*) depressed serum complement; (*3*) endocapillary proliferative and exudative GN on LM; (*4*) C3-dominant or codominant glomerular staining on IF; and (*5*) hump-shaped subepithelial deposits on EM.[9] Thirteen patients with presumed PIGN were excluded from this study because they fulfilled only two of these diagnostic criteria. The remaining 80 patients fulfilled at least three criteria. Among these, 25 (31%) fulfilled five of five criteria, 34 (42%) fulfilled four of five criteria, and 21 (26%) fulfilled three of five criteria. These 80 patients, in addition to the 29 patients aged ≥65 years that we recently reported from Columbia University,[9] form the basis of this report.

Standard processing of renal biopsies included LM, IF, and EM. For LM, all samples were stained with hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome, and Jones methenamine silver. For IF, 3-μm cryostat sections were stained with polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinogen, and albumin (Dako Corp., Carpinteria, CA).

Clinical data, including demographic information, presenting clinical and laboratory findings, medical history, treatment and follow-up, were obtained from referral forms submitted at the time of biopsy, patients' medical records, and telephone interviews with the referring nephrologist. The following clinical definitions were used: NRP ≥3.0 g/d; hypoalbuminemia, serum albumin <3.5 g/dl; renal insufficiency, serum creatinine >1.2 mg/dl; nephrotic syndrome, NRP, hypoalbuminemia, and peripheral edema; and hypertension, systolic BP >140 mmHg, diastolic BP >90 mmHg, or ongoing treatment with antihypertensive medications. For outcome analysis, CR was defined as normalization of serum creatinine to baseline levels or to a creatinine ≤1.2 mg/dl (for those patients in whom baseline creatinines were unavailable); PRD was defined by elevation of serum creatinine 0.2 mg/dl above baseline levels or follow-up creatinine >1.2 mg/dl (for those in whom baseline levels were unavailable); and ESRD was defined as requiring renal replacement therapy.

The degree of DGS was graded according to the recently published Renal Pathology Society classification.[18] Tubular atrophy and interstitial fibrosis were graded on a semiquantitative scale on the basis of 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). Acute tubular injury, interstitial edema, and interstitial inflammation were graded on a semiquantitative scale on the basis of an estimate of the percentage of renal cortex affected and recorded as: 0 (none), 1% to 50% (focal), or >50% (severe).

Continuous variables are reported as the means ± SD. Statistical analysis was performed using SPSS for Windows®, version 16.0 (SPSS, Chicago, Illinois). Analysis was performed using nonparametric exact statistical methods. Univariate analysis was performed using the Mann-Whitney-Wilcoxon test, the Kruskal-Wallis test, and the Fisher-Freeman-Halton exact test, as appropriate for variable type. Multivariate analysis was performed using binary and ordinal logistic regression analysis. Survival analysis for progression to ESRD was performed by the method of Kaplan and Meier using the log rank test for univariate analysis and the Cox proportional hazards model for multivariate analysis. Statistical significance was assumed at $P < 0.05$. The study was approved by the institutional review boards of the Mayo Clinic Foundation and Columbia University.

DISCLOSURES

None.

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