

Incidental Healed Postinfectious Glomerulonephritis: A Study of 1012 Renal Biopsy Specimens Examined by Electron Microscopy

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Glomerulonephritis (GN) characterized by immune complex deposits typical of postinfectious GN but with a paucity or absence of overt clinical symptoms and/or urinary abnormalities may occur after a group A streptococcus infection. The overall incidence of this type of subclinical GN is not known. To address this question, electron microscopy findings in 1012 consecutive renal biopsy specimens (952 native kidney, 60 transplant) examined by a single renal pathologist from August 1999 to April 2002 were retrospectively reviewed for the presence of distinct subepithelial and intramembranous deposits indicative of postinfectious GN. Such deposits were noted in 83 biopsy specimens, including 26 with a primary diagnosis of postinfectious GN (acute, persistent, or latent) and 57 in which these deposits were an incidental finding. In each of the latter 57 cases, some or all of the deposits showed partial or extensive loss of electron density typical of partially or largely resorbed deposits. A diagnosis of incidental postinfectious GN was not made in any biopsy specimen exhibiting another immune complex-related glomerular disease that could possibly account for the deposits, composing 443 of the 1012 biopsy specimens examined. Thirty of the 57 biopsy specimens with incidental postinfectious GN showed mesangial hypercellularity, although this was focal and segmental in all but 3 cases

Postinfectious glomerulonephritis (GN) is an immune complex-mediated disease occurring most commonly after a group A streptococcus infection. In its classic acute form, patients develop macroscopic hematuria and facial and/or lower extremity edema 1 to 4 weeks after the infection, in some cases with associated hypertension and oliguria.¹ Histologically, there is a diffuse proliferative and often exudative GN, with granular deposits of IgG and C3 in glomerular capillary loops and mesangial areas detected by immunofluorescence (IF) and the characteristic electron microscopy finding of large subepithelial electron-dense deposits or "humps," typically with mesangial and subendothelial deposits.¹ Although classic cases of postinfectious GN are easily recognized clinically, considerable evi-

and was not accompanied by the endocapillary hypercellularity typical of acute postinfectious lesions. Immunofluorescence microscopy revealed glomerular deposits of C3 in >90% of these biopsy specimens and IgM deposits in 66%, but only rare IgG, IgA, and C1q deposits. Twenty-three (40%) of these 57 biopsy specimens exhibited diabetic nephropathy, either alone or in combination with another lesion; for perspective, only 128 (13%) of the 1012 biopsy specimens examined showed evidence of diabetic nephropathy. In summary, incidental evidence of resolving or largely healed postinfectious GN was noted in up to 10.5% of renal biopsy specimens (57 of 543, not including specimens with a primary diagnosis of an immune complex-related glomerular disease). The recognition of such lesions is potentially important in the interpretation of certain renal biopsy specimens. HUM PATHOL 34:3-10. Copyright 2003, Elsevier Science (USA). All rights reserved.

Key words: poststreptococcal glomerulonephritis, electron microscopy, renal biopsy, hematuria, diabetic nephropathy.

Abbreviations: ANCA, antineutrophil cytoplasmic autoantibody; ASO, antistreptolysin O; EM, electron microscopy; GN, glomerulonephritis; IF, immunofluorescence; LM, light microscopy.

dence indicates that a significant number of patients who do not manifest typical clinical features of postinfectious GN after a streptococcal infection nevertheless develop a subclinical form of postinfectious GN with glomerular immune complex deposits, including subepithelial "humps" in some cases.^{2,3}

Although the great majority of patients (especially children) with acute postinfectious GN make a complete clinical recovery,^{1,4,5} a significant number continue to exhibit urinary abnormalities (e.g., subnephrotic range proteinuria, microscopic hematuria) months to years after the initial disease onset.⁵⁻⁸ Furthermore, even in patients with no or only very minor urinary abnormalities months to years after an episode of acute postinfectious GN, morphologic abnormalities of glomeruli often persist. These abnormalities include mesangial hypercellularity and matrix expansion, deposits of C3 and (to a lesser extent) immunoglobulins detected by IF mainly in the mesangium, and partially or largely resorbed subepithelial/intramembranous and mesangial deposits on electron microscopy (EM), with associated irregularities of the glomerular basement membrane.^{1,8-11}

The presence of residual immune complex deposits from a largely healed postinfectious lesion can com-

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uplicate interpretation of renal biopsy specimens,¹² particularly when clinical history does not suggest previous postinfectious GN. At our renal biopsy service, cases in which EM findings suggest old postinfectious lesions are not uncommon; however, this phenomenon has never been documented in a large series of renal biopsy specimens. Consequently, this study aims to determine the frequency with which incidental ultrastructural findings of largely healed postinfectious GN are observed in a series of consecutive renal biopsy specimens, and to determine whether these findings tend to occur with higher than expected frequency in association with any other renal diseases.

PATIENTS AND METHODS

Computerized records from the Department of Pathology of Johns Hopkins Hospital were reviewed to identify all renal biopsy specimens received at the Johns Hopkins renal biopsy service from August 1999 through April 2002 and analyzed by a single renal pathologist (M.H.) using EM. A total of 1012 such biopsy specimens were identified, including 952 native kidney specimens and 60 renal transplant specimens. No repeat biopsy specimens were included. Approximately 95% of the specimens were from patients ≥ 18 years old. In each of these cases, EM examination of a specimen containing between 1 and 3 glomeruli and photography of representative and specific, diagnostic and incidental ultrastructural findings were performed by the aforementioned pathologist (M.H.).

For each of these 1012 cases, the renal biopsy reports were reviewed to identify biopsy specimens in which the presence of subepithelial and/or intramembranous immune complex-type deposits was noted, but where the primary renal biopsy diagnosis was not an immune complex-related glomerular lesion that could potentially account for the deposits present. For these latter biopsy specimens, the electron micrographs were reviewed; in 57 cases the following criteria suggestive of a resolving or largely resolved postinfectious GN were met: (1) an average of 3 or more (but not so numerous as to suggest membranous nephropathy) distinct subepithelial or intramembranous deposits per glomerulus examined, including deposits within the basement membrane overlying mesangial regions, with some or all of these deposits showing evidence of resorption (i.e., areas of electron-lucency and/or microvesicular change), and (2) no specific substructure in the deposits suggestive of a disease other than postinfectious GN (e.g., cryoglobulinemia, fibrillary GN, "fingerprints" suggestive of lupus nephritis). In the clinical data provided at the time of biopsy, none of the 57 patients was noted to have a history of clinically documented or biopsy-proven postinfectious GN.

The 1012 cases examined also included 26 with a primary diagnosis of postinfectious GN. For these cases, the postinfectious GN was classified as acute/subacute, persistent/progressive, or healed/latent based on the following morphologic and clinical criteria:

1. *Acute/subacute GN* included cases with diffuse mesangial and endocapillary hypercellularity detected by light microscopy, multiple subepithelial "humps" detected by EM, and a clinical presentation of acute or subacute renal insufficiency with a nephritic urine sediment or an acute nephritic syndrome with mild renal insufficiency.

2. *Persistent/progressive GN* included cases with active endocapillary and/or mesangial proliferative GN with clinical symptoms of glomerular disease of more than 2 months' duration, or with a clinical presentation consistent with acute/subacute GN but no diffuse mesangial and endocapillary hypercellularity in the biopsy specimen.
3. *Healed/latent GN* was diagnosed in cases showing IF and EM findings most compatible with postinfectious GN (i.e., predominant granular C3 deposits by IF; distinct, relatively large, often partially or largely resorbed subepithelial and/or intramembranous deposits with no prominent subendothelial deposits by EM) but no more than mild mesangial hypercellularity by light microscopy. In the great majority of these cases, the clinical presentation was subnephrotic range proteinuria and/or microscopic hematuria with stable renal function.

For each of the 57 cases with incidental ultrastructural evidence of resolving postinfectious GN and the 26 cases with a primary diagnosis of postinfectious GN, the renal biopsy reports and clinical data provided at the time of the biopsy were again reviewed, and the following data were recorded: primary renal biopsy diagnosis or diagnoses; IF findings for IgG, IgA, IgM, C3, and C1q; patient age, sex, and race; presence or absence of hematuria and of hypertension; and serum C3 levels if available. In addition, histologic slides from each biopsy specimen were reviewed and graded for the presence or absence of mesangial and endocapillary hypercellularity, and when present, whether these were diffuse or focal and segmental. All study procedures were approved by the Johns Hopkins Hospital Joint Committee on Clinical Investigation.

RESULTS

Frequency of Incidental Healed Postinfectious GN and Association With Other Diseases

Of the 1012 biopsy specimens examined (952 native kidney and 60 transplant), 83 showed ultrastructural evidence of postinfectious GN. In 26 of these cases, this was the sole or primary renal biopsy diagnosis, with 9 of these biopsy specimens showing an acute or subacute lesion, 7 a persistent or progressive lesion, and 10 a largely healed or latent lesion. Nineteen of these biopsy specimens were from adults (age range, 18 to 82), and 7, all with persistent/progressive or healed/latent lesions, were from children (age range, 8 to 17). In 57 cases, findings of a largely healed postinfectious GN were noted incidentally; this group comprised 5.8% of the biopsy specimens without postinfectious GN as a primary diagnosis. Table 1 lists the clinical indications for renal biopsy in these 83 cases.

For biopsy specimens with a primary diagnosis of postinfectious GN, the presenting symptoms together with morphologic findings were used to identify the type of lesion present (see Patients and Methods). Cases of acute/subacute GN presented with active urine sediment (red blood cells and red blood cell casts) and often with acute renal failure. Persistent/progressive lesions most often presented with chronic (or progressive) renal insufficiency and proteinuria.

TABLE 1. Indications for Renal Biopsy in Cases of Postinfectious GN

	Number (Percentage) of Cases			
	Incidental	Acute/ Subacute	Persistent/ Progressive	Healed/Latent
Acute/subacute renal failure	22 (39%)	6 (67%)	1 (14%)	0
Chronic renal failure + subnephrotic proteinuria	12 (21%)	0	2 (29%)	0
Chronic renal failure + nephrotic proteinuria	8 (14%)	0	1 (14%)	1 (10%)
Nephrotic syndrome or nephrotic proteinuria	9 (16%)	0	0	0
Acute nephritic syndrome + mild renal insufficiency	0	3 (33%)	0	0
Subnephrotic proteinuria + hematuria	0	0	2 (29%)	7 (70%)
Subnephrotic proteinuria	4 (7%)	0	0	1 (10%)
Microscopic \pm gross hematuria	1 (2%)	0	0	1 (10%)
Renal insufficiency of unknown duration	1 (2%)	0	1 (14%)	0
Total Cases	57	9	7	10

NOTE. Nephrotic proteinuria is defined as proteinuria of ≥ 3.5 g/day.

Most healed/latent lesions presented with subnephrotic-range proteinuria and/or microscopic hematuria and stable renal function. For the 57 cases with an incidental finding of largely healed postinfectious GN, the clinical indications for biopsy reflected the primary diagnosis (Table 2), with the most common indications being acute or chronic renal insufficiency and proteinuria, in some cases with nephrotic syndrome.

Table 2 lists the primary diagnoses in the 57 cases with incidental postinfectious GN, all but 1 of which were native kidney biopsy specimens. It is of interest that 23 (40%) of these biopsy specimens exhibited diabetic nephropathy, either alone or in combination with another lesion [e.g., interstitial nephritis, antineutrophil cytoplasmic autoantibody (ANCA)-associated necrotizing/crescentic GN]. In comparison, 128 (13%) of the 1012 total biopsy specimens showed evidence of diabetic nephropathy. Notably, we did not attempt to diagnose incidental postinfectious GN in 443 biopsy

specimens that showed another immune complex-related glomerular disease (e.g., lupus nephritis, IgA nephropathy, membranous nephropathy), because these conditions could possibly account for all of the immune complex deposits present. As such, the percentage of 5.8% noted earlier probably underestimates the frequency of incidental postinfectious GN in our biopsy population—it may in fact be as high as 10.5% (57 of 543). The mean age of the 57 patients with incidental largely healed postinfectious GN was 56 + 15 (standard deviation) years, with a range of 21 to 85 years. Thirty-three of the patients were male and 24 were female; 36 were white, 19 were African-American, 1 was Hispanic, and 1 was Asian-American. Thirty-six patients had hematuria, although only 1 patient (with a primary diagnosis of thin glomerular basement membrane nephropathy) had macroscopic hematuria. Excluding patients with ANCA-associated GN, no patients had red blood cell casts in their urine. Thirty-nine of the 57 patients had a history of hypertension. Of 23 patients for whom serum C3 levels were available, 18 had levels within the normal range and 5 had levels below this range.

TABLE 2. Primary Diagnoses of 57 Renal Biopsies Showing Incidental Postinfectious GN

Diagnosis	Number of Cases
Diabetic nephropathy	17
Focal-segmental glomerulosclerosis*	7
ANCA-associated necrotizing/crescentic GN	6
Interstitial nephritis (drug-induced)	6
Diabetic nephropathy and interstitial nephritis	5
Light chain cast nephropathy	3
Malignant and/or advanced nephrosclerosis	3
Acute tubular necrosis (ischemic or rhabdomyolysis-related)	2
Acute pyelonephritis	1
ANCA-associated GN and diabetic nephropathy	1
ANCA-associated GN and interstitial nephritis	1
Human immunodeficiency virus-associated nephropathy	1
Minimal change nephropathy	1
Minimal change nephropathy and interstitial nephritis	1
Tacrolimus nephrotoxicity (status post-liver transplant)	1
Thin glomerular basement membrane nephropathy	1

*Includes 1 case of recurrent focal-segmental glomerulosclerosis in a cadaveric renal allograft.

Pathologic Features

By light microscopy, nearly half of the biopsy specimens with incidental largely healed postinfectious lesions had normocellular glomeruli. The remainder showed mesangial hypercellularity that in most cases was mild, focal, and segmental (Table 3; Fig 1G). Some glomeruli contained small numbers of mononuclear leukocytes (Fig 1D), but none of these biopsy samples had significant numbers of glomerular neutrophils or true endocapillary cell proliferation. One biopsy specimen exhibited rare fibrous crescents; however, no cellular crescents were observed except in cases where the primary diagnosis was ANCA-associated GN. As shown in Table 3, glomerular histology in these 57 cases was quite similar to that in the 10 cases in which the primary diagnosis was healed or latent postinfectious GN, and contrasted with that in cases of acute and subacute postinfectious GN that uniformly showed diffuse mes-

TABLE 3. Patterns of Glomerular Hypercellularity in Cases of Postinfectious GN

Type (Number) of GN	Number (Percentage) of Biopsies Showing					
	Diffuse Mesangial and EC, Exudative	Diffuse Mesangial and EC	Diffuse Mesangial	Focal/Segmental Mesangial and EC	Focal/Segmental Mesangial	Normal Cellularity
Incidental (57)	0	0	3 (5%)	0	27 (47%)	27 (47%)
Acute/subacute (9)	7 (78%)	2 (22%)	0	0	0	0
Persistent/progressive (7)	1 (14%)	2 (29%)	3 (43%)	1 (14%)	0	0
Healed/latent (10)	0	0	0	0	4 (40%)	6 (60%)

Abbreviation: EC, endocapillary.

NOTE. The number of biopsies in each diagnostic category is indicated in parentheses.

angial and endocapillary hypercellularity, in most cases with prominent numbers of glomerular neutrophils (exudative GN).

Nearly all cases (52 of 56; 93%) of incidental largely healed postinfectious GN showed glomerular immune deposits by IF, usually consisting of IgM and C3 or C3 alone, with only small numbers of cases staining positively for IgG, IgA, and/or C1q (Table 4). In most cases the deposits were limited to mesangial regions, although 32% of cases showed peripheral capillary C3 deposits (Table 4; Fig 1B and H). In half of the cases, the intensity of C3 staining was >1+ on a scale of 0 to 4+, although staining of this intensity for immunoglobulins was uncommon (16% of cases, all for IgM; Table 4). A similar C3 predominance was observed in those 10 cases in which the primary diagnosis was healed or latent postinfectious GN (Table 4).

By EM, all 57 cases of incidental, largely healed postinfectious GN showed subepithelial and/or intramembranous deposits of varying size and electron density (Fig 1C, F, and I). The great majority of these biopsy specimens also showed generally modest mesangial deposits; however, subendothelial deposits were only rarely seen and were never prominent (Table 5). The number of subepithelial/intramembranous deposits per glomerulus ranged from 3 to approximately 20; the latter case is depicted in Fig 1A to C. In most cases the number of such deposits was fewer than 10 per glomerulus. As shown in Table 5, in most cases of incidental postinfectious GN, subepithelial deposits were located within or between folds of the glomerular basement membrane overlying mesangial regions [the so-called mesangial "notch" or "waist" (Fig 1C and F)], as has been described in resolving postinfectious GN.^{11,13} These ultrastructural findings are thus consistent with the predominantly mesangial pattern of C3 deposition seen by IF (Table 4). The pattern of deposits seen by EM in the 57 cases with incidental postinfectious GN is similar to that observed in the 10 cases with a primary diagnosis of healed or latent postinfectious GN (Table 5). Although subepithelial "notch" deposits were also seen in the overwhelming majority of biopsy specimens with acute/subacute and persistent/progressive postinfectious GN (Table 5), most of these biopsy specimens also showed subendothelial deposits, and all acute/subacute lesions had varying numbers of subepi-

thelial "humps" underlying portions of the glomerular basement membrane not adjacent to the mesangium.

DISCUSSION

It is well documented that morphologic lesions of postinfectious GN with no overt clinical symptoms and/or no more than minor urinary abnormalities may occur after group A streptococcus infection.^{2,3,14-16} Indeed, Sagel et al² prospectively studied urine samples from 248 children after infections with group A streptococci, and found that 35 (14%) developed minor urinary abnormalities (proteinuria of <150 mg/dL and/or microscopic hematuria), with transient depression of serum complement levels in 20 of these 35 children. These 20 children underwent renal biopsy; specimens from 19 exhibited histologic abnormalities of the glomeruli ranging from mild, focal, and segmental mesangial hypercellularity and matrix expansion (7 cases) to diffuse mesangial proliferative GN (9 cases) and even diffuse proliferative and exudative GN typical of acute postinfectious GN (3 cases). Fifteen of the biopsy specimens demonstrated granular glomerular capillary loop and mesangial deposits of IgG and C3 by IF. Mesangial, subepithelial, and/or intramembranous deposits were seen in 5 of 12 biopsy specimens examined by EM. But only 1 of the 35 children with minor urinary abnormalities showed any overt symptoms suggestive of postinfectious GN; this child, with a biopsy specimen exhibiting diffuse proliferative and exudative GN, developed periorbital edema for 2 days.²

In the present study, ultrastructural evidence of healed or largely healed postinfectious GN was noted in 57 of 986 (5.8%) consecutive renal biopsy specimens examined by a single pathologist, not including 26 biopsy specimens with postinfectious GN as a primary diagnosis. Although this seems to be a rather high percentage, it may actually be an underestimate of the true figure. This could result from the fact that it was not considered justified to diagnose healed postinfectious GN in biopsy specimens with a primary diagnosis of immune complex-related glomerular disease (443 of the 986 cases) and that in some (if not most) cases of postinfectious GN, complete resolution of immune complex deposits eventually occurs.^{6,11,17,18} Nonethe-

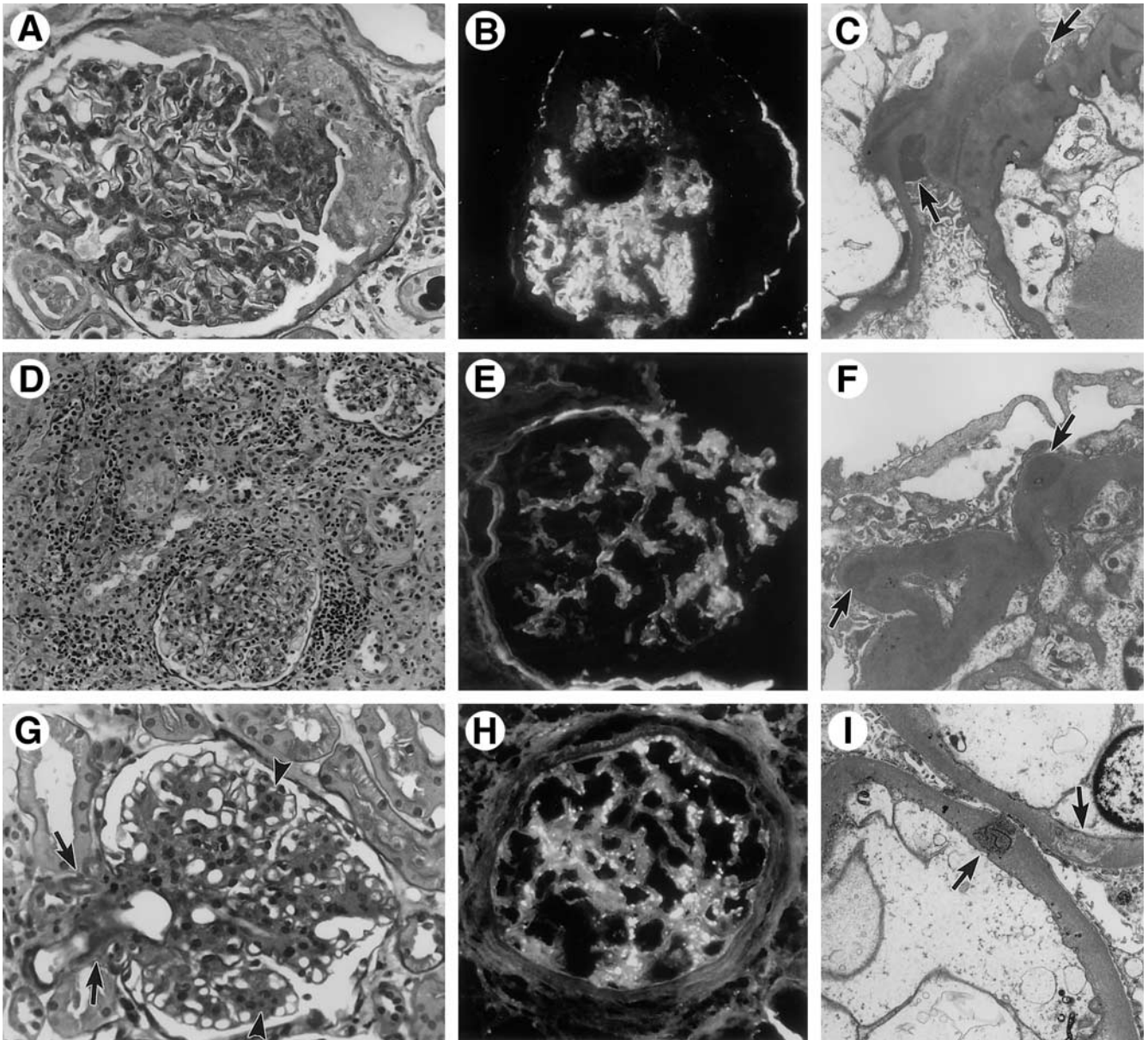


FIGURE 1. Histologic, IF, and EM findings in 3 biopsies showing incidental largely healed postinfectious GN. (A, B, and C) Biopsy specimen with primary diagnosis of ANCA-associated necrotizing and crescentic GN. (A) The glomerulus exhibits a cellular crescent but no more than very mild and segmental mesangial hypercellularity. (B) IF shows C3 staining (3+ on a scale of 0 to 4+) in the mesangium and capillary loops of a glomerular tuft compressed by a large crescent; there is also staining of Bowman's capsule. (C) EM shows 2 subepithelial deposits in "notch" regions underlying the mesangium (arrows). (D, E, and F) Biopsy specimen with a primary diagnosis of drug-induced interstitial nephritis. (D) By LM, the glomeruli contain occasional mononuclear leukocytes but are otherwise normocellular. (E) IF shows 1+ granular mesangial C3 staining. (F) EM shows 2 partially resorbed intramembranous deposits (arrows), again underlying a mesangial area. (G, H, and I) Biopsy specimen with primary diagnosis of diabetic nephropathy (diffuse glomerulosclerosis). (G) Histologically, there is a moderate increase in mesangial matrix and a mild, segmental increase in mesangial cellularity (arrowheads). Hyaline change is seen in both afferent and efferent arterioles (arrows). (H) IF shows granular mesangial and capillary loop staining for C3 (2+). (I) EM shows 2 extensively resorbed intramembranous deposits (arrows); the deposit within the lower basement membrane is interpreted as showing striated membrane structures or possibly cellular elements, as have been described by Tomroth¹⁰ within foci of resorbed deposits in resolving postinfectious GN. The glomerular basement membranes are thickened. Compare this with (C), which is of the same magnification. ((A and G) Periodic acid-Schiff stain, original magnification $\times 400$; (D) periodic acid-Schiff stain, original magnification $\times 200$; (B, E, and H) direct immunofluorescence with fluorescein isothiocyanate-conjugated goat anti-human C3, original magnification $\times 400$; (C and I) uranyl acetate and lead citrate stain, original magnification $\times 6300$; (F) uranyl acetate and lead citrate, original magnification $\times 8000$.)

TABLE 4. Glomerular Immunofluorescence Findings in Cases of Postinfectious GN

Type (Number) of GN	IgG			IgA			IgM			C3			C1q		
	M	M,L	>1+	M	M,L	>1+	M	M,L	>1+	M	M,L	>1+	M	M,L	>1+
Incidental (56)	2	1	0	1	0	0	32	5	9	34	18	28	5	1	0
Acute/subacute (8)	0	7	5	2	4	1	3	5	3	0	8	8	1	3	1
Persistent/progressive (7)	0	3	3	0	0	0	3	3	3	1	6	7	1	3	0
Healed/latent (10)	0	0	0	1	0	0	7	0	1	3	6	5	2	1	0

NOTE. Data shown are the number of biopsies in each category showing mesangial only (M) or mesangial plus capillary loop (M,L) staining by direct IF using antibodies to each immunoglobulin type or complement component listed, and the number of biopsies with staining intensity > 1+ (mesangial or combined mesangial and capillary loop) on a 0 to 4+ scale. The number of biopsies tested in each category is listed in parentheses; 1 biopsy in each of the “incidental” and “acute/subacute” categories contained no glomeruli for IF study.

less, these findings should not be entirely surprising—after all, streptococcal infections remain quite common. In a study of 600 healthy male military recruits in 1989, 106 (18%) had serologic evidence of a recent group A streptococcal infection [anti-streptolysin O (ASO) titer >400] at the time they entered training camp.¹⁹ Furthermore, according to the study by Sagel et al,² as many as 14% of people with group A streptococcal infections will develop evidence of postinfectious GN, the great majority of whom with no overt clinical symptoms. Finally, the patient population in the present study is clearly not representative of the general population, and most notably included a prominent percentage (13%) of patients with diabetic nephropathy. The fraction of biopsy specimens with incidental postinfectious GN that also exhibited diabetic nephropathy (23 of 57; 40%) was considerably greater than 13%, perhaps related to diabetes mellitus being a known risk factor for group A streptococcal infection.^{20,21} However, it is also quite possible that this may reflect, at least in part, a higher renal biopsy rate among those patients with diabetic nephropathy in whom the clinical presentation may have suggested the possibility of an additional lesion. Whereas in each of the 57 cases showing incidental healed or largely healed postinfectious GN, the major clinical findings

could be fully accounted for by the primary renal biopsy diagnosis or diagnoses, the postinfectious lesion might have accounted for the microscopic hematuria present in some cases and for the decreased serum C3 level seen in 5 cases.

Curiously, only 1 of 60 biopsy specimens of transplanted kidneys that were examined ultrastructurally showed evidence of previous postinfectious GN. This may simply be coincidental, although numerous additional factors could be involved. First, most renal transplants performed at our center over the past several years have been live-donor transplants, and potential donors are carefully screened to exclude persons with any evidence of renal disease, including abnormal urinary findings. In the present study, 36 of 57 patients with incidental findings of previous postinfectious GN had microscopic hematuria at the time of biopsy; this was clearly related to the primary renal disease present in some—but probably not all—cases. Furthermore, a significant number of patients with healed postinfectious GN have been found to have low-grade proteinuria and/or hypertension as long as 10 to 15 years after the acute disease, even in the absence of residual immune complex deposits detectable by IF and/or EM.⁶ Second, it is possible that the prophylactic antibiotics and immunosuppressive agents used in our transplant recipients act to reduce the incidence of group A streptococcal infections and of subclinical postinfectious GN in this patient population.

In this study, the presence of incidental healed or healing postinfectious GN was defined on the basis of EM findings showing partially resorbed subepithelial and/or intramembranous deposits, which Tornroth¹⁰ found to persist in a large fraction of cases and Rosenberg et al¹¹ found in a smaller but significant fraction of cases of postinfectious GN months to years after the acute disease, often in the absence of hematuria and proliferative changes within glomeruli by LM. In 88% of cases we also found segmental mesangial deposits, which also tend to persist well beyond the acute phase of the disease;^{11,13} however, only very rarely did we find subendothelial deposits, which are usually absent more than 5 weeks after the initial symptoms of acute postinfectious GN.¹³ Many of the subepithelial/intramembranous deposits were located in mesangial “notch” or “waist” regions. Heptinstall²² first emphasized that in

TABLE 5. Ultrastructural Location of Deposits in Cases of Postinfectious GN

Type of GN (Number)	Number (Percentage) of Biopsies Showing*		
	Subepithelial Deposits in Mesangial “Notch”	Mesangial Deposits	Subendothelial Deposits
Incidental (57)	41 (72%)	50 (88%)	5 (9%)†
Acute/subacute (9)	9 (100%)	9 (100%)	9 (100%)
Persistent/progressive (7)	6 (86%)	7 (100%)	4 (57%)
Healed/latent (10)	7 (70%)	10 (100%)	3 (30%)†

*In addition to the deposits noted here, biopsies showed varying numbers of peripheral subepithelial and/or intramembranous deposits, with definitive subepithelial “humps” in all cases of acute/subacute GN.

†In each of these cases the subendothelial deposits were very rare and showed evidence of partial resorption.

acute postinfectious GN, subepithelial deposits tend to be most plentiful in these regions of the glomeruli, and Sorger et al¹³ later found that deposits in this location persisted for longer than subepithelial deposits underlying peripheral capillary basement membranes, thus apparently accounting for the predominantly mesangial pattern of C3 staining by IF typically seen beyond 6 weeks after the onset of postinfectious GN. Sorger et al¹³ also found that in these later postinfectious lesions, C3 staining was most often present with little or no accompanying immunoglobulin, as was the case in most of the 57 cases of incidental postinfectious GN (as well as in 8 of the 10 biopsy specimens showing healed/latent postinfectious GN as a primary diagnosis) in this study.

A potential shortcoming of this study is that the diagnosis of incidental healed or healing postinfectious GN was based entirely on morphologic findings that are not entirely specific for postinfectious GN, although in 41 of our 57 cases there were subepithelial deposits in mesangial “notch” regions, which are strongly suggestive of postinfectious GN.^{11,13,22} It is not known how many of the patients had a documented streptococcal infection at some point in their past, and pertinent serologic data (e.g., ASO titers, serum C3 levels) were not available for many of the patients (in part because postinfectious GN was not suspected clinically in these cases). Still, with lesions of postinfectious GN that in some instances are likely to be several years old, the completeness and/or accuracy of information regarding remote streptococcal infections may be limited, as is the correlative value of serologic markers such as ASO titers and serum C3 levels obtained at the approximate time of biopsy. Just over 50% of the biopsy specimens with incidental healed or healing postinfectious GN showed mesangial proliferative changes by LM, and resolving postinfectious GN is just 1 of the multiple diseases potentially associated with mesangial proliferative GN.²³ Among the major primary and secondary forms of mesangial proliferative GN reviewed in 1982 by Cohen and Border,²³ including controversial entities such as IgM nephropathy, the only lesion that can consistently account for the combination of subepithelial/intramembranous deposits with absent or only very rare subendothelial deposits by EM and predominant C3 staining by IF is healing postinfectious GN. However, since that time, there have been several reports of mesangial proliferative GN with isolated C3 deposits (i.e., C3 mesangial proliferative GN),^{24,25} with subepithelial deposits identified by EM in a minority (<20%) of these cases.²⁵ Nonetheless, C3 mesangial proliferative GN remains a poorly defined entity, and at least some of these cases are likely to represent largely healed postinfectious lesions.²⁶

From a diagnostic pathologist’s standpoint, perhaps the most important aspect of this study is that incidental healed or healing postinfectious GN may overlap with other glomerular diseases, including ANCA-associated (pauci-immune) crescentic GN. The recognition of overlapping ANCA-associated crescentic and healing postinfectious GN, and its distinction from

active crescentic postinfectious GN, may have important clinical implications. As with the distinction of overlapping mild IgA nephropathy and ANCA-associated crescentic GN from crescentic IgA nephropathy,²⁷ a key differentiating feature is the pattern and extent of glomerular tuft hypercellularity by LM. Although some cases of healing or healed postinfectious GN may show significant numbers of subepithelial “humps” by EM and even diffuse mesangial hypercellularity, none of the 57 cases of incidental postinfectious GN identified in this study had diffuse mesangial and endocapillary hypercellularity. In contrast, this was seen in all 9 cases of acute or subacute postinfectious GN, most of which had an exudative component.

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