Staphylococcus Infection-Associated Glomerulonephritis Mimicking IgA Nephropathy

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The association of methicillin-resistant *Staphylococcus aureus* (MRSA) infection with glomerulonephritis (GN) has been well documented in Japan but not in North America. Recently, eight renal biopsies with IgA-predominant or -codominant GN from eight patients with underlying staphylococcal infection, but without endocarditis, were observed at a single institution in a 12-mo period. Renal biopsies were worked up by routinely used methodologies. Eight cases of primary IgA nephropathy were used as controls. Five patients had MRSA infection, one had methicillin-resistant *S. epidermidis* (MRSE) infection, and two had methicillin-sensitive *S. aureus* infection. Four patients became infected after surgery; two patients were diabetic and had infected leg ulcers. All patients developed acute renal failure, with active urine sediment and severe proteinuria. Most renal biopsies showed only mild glomerular hypercellularity. Two biopsies had prominent mesangial and intracapillary hypercellularity; one of them (the MRSE-associated case) had large glomerular hyalin thrombi. This patient also had a positive cryoglobulin test. Rare glomerular hyalin thrombi were noted in two other cases. Immunofluorescence showed IgA pre- or codominance in all biopsies. Electron microscopy revealed mesangial deposits in all cases. Five biopsies had rare glomerular capillary deposits as well. In the MRSE-associated GN, large subendothelial electron-dense deposits were present. These cases demonstrate that staphylococcal (especially MRSA) infection-associated GN occurs in the US as well, and a rising incidence is possible. It is important to differentiate a *Staphylococcus* infection-associated GN from primary IgA nephropathy to avoid erroneous treatment with immunosuppressive medications.

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Staphylococci are widespread pathogens and their frequent antibiotic resistance makes treatment difficult. Occasional episodes of glomerulonephritis (GN) after *Staphylococcus epidermidis* bacteremia in patients with ventriculoatrial or ventriculojugular shunts and after *S. aureus* bacteriemia secondary to endocarditis are well documented and are discussed in most nephrology and renal pathology textbooks. These *Staphylococcus* infection-related glomerulonephritides are associated with glomerular immune complex deposits, which contain complement (mainly C3) IgG and sometimes IgM. Much less is known about GN associated with methicillin-resistant *S. aureus* (MRSA), and methicillin-resistant *S. epidermidis* (MRSE), which are now endemic in most hospitals. A growing number of community-acquired infections are also reported (1).

The association of MRSA infection with GN has been well documented in Japan (2–9). Based primarily on these publications, it appears evident that *S. aureus*-associated GN is characterized by glomerular IgA deposits; therefore, the renal biopsy findings strongly resemble primary (idiopathic) IgA nephropathy. The IgA-containing immune complexes are mainly deposited in the mesangium, but they may be encountered along the glomerular capillaries as well. Only anecdotal reports are known on *S. aureus* infection and GN with IgA deposits from Europe and the US (10–14). The largest series to date (14) describes five patients with type II diabetes mellitus who developed proliferative GN with IgA-dominant immune complex deposits. At our institution, we have encountered eight patients with *Staphylococcus* infection-associated mesangial and/or intracapillary proliferative GN with IgA-predominant or -codominant glomerular immune complex deposits within a 12-mo period. Only two of these patients had underlying diabetes mellitus. None of the patients had endocarditis. The purpose of our study is to draw attention to *Staphylococcus* infection-associated GN, which can be easily misdiagnosed as idiopathic IgA nephropathy and lead to incorrect treatment.

Materials and Methods

Cases

Between October 1, 2004, and October 1, 2005, we identified eight patients with *Staphylococcal* infection-associated GN whose biopsies showed glomerular predominant or codominant IgA immune complex deposits. *S. aureus* endocarditis-associated GN cases were not included. As a control group, we included eight cases of primary IgA mesangioproliferative GN that had typical clinical presentation, morphology, and clinical course, and were identified during the study period. All patients were white except for one of the controls with primary IgA nephropathy, who was black.

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Biopsy Processing

Renal biopsies were triaged and processed for light microscopy, electron microscopy, and immunofluorescence (IF). For light microscopy, sections were fixed in 10% buffered formaldehyde and embedded in paraffin. For immunofluorescence, a portion of the tissue was placed in optimal cutting temperature (OCT) embedding compound (Tissue-Tek, Sakura Finetek, Torrance, CA) and frozen in liquid nitrogen. Frozen sections were stained by direct IF methodology using antibodies to human IgG, IgA, IgM, κ and λ light chains, C1q, C3, C4, fibrinogen, and albumin (Dako Cytomation, Carpenteria, CA). We also used monoclonal antibodies to IgA1 and IgA2 (Novus Biologicals, Littleton, CO) with an indirect IF methodology. The secondary antibody was goat $F(ab')_2$ fragment anti-mouse Ig (H+L)-FITC–conjugated (Beckman Coulter, Somerset, NJ). For electron microscopy, the tissue was fixed in 3% buffered glutaraldehyde and embedded in epoxy resin. Thin sections were contrasted with uranyl acetate and lead citrate.

Histologic and IF Evaluation

Scoring of the chronic tubulointerstitial injury was based on the percentage of interstitial fibrosis and tubular atrophy in the renal cortex. If interstitial fibrosis and tubular atrophy involved <25% of the renal cortex, the fibrosis was graded as mild (1+); 25 to 50% involvement was graded as moderate (2+); if >50% of the renal cortex was involved, the fibrosis was graded as severe (3+). Other histologic parameters were also scored semiquantitatively on a scale from 0 to 3+. Intensity of IF staining was graded from 0 to 3+ (absent, mild, moderate, and strong).

Results

Between October 1, 2004, and October 1, 2005, 501 adult native kidney biopsies were evaluated by our nephropathology laboratory. Eight of these biopsies (1.6%) were diagnosed to have IgA predominant or codominant immune complex GN associated with *Staphylococcus* infection. Five patients had MRSA, one patient had MRSE, and two patients had methicillin-sensitive *S. aureus* (MSSA) infection. The clinical characteristics of the patients are provided in Table 1. Most patients were male and elderly, with severe underlying conditions. Only two of the eight patients were diabetic, and both of them had prominent diabetic nephropathy with nodular diabetic glomerulosclerosis. Both patients had infected leg ulcers. One patient needed surgery for an epidural abscess after endocarditis. One patient developed wound infection after a motor vehicle accident and the remaining four patients developed infectious complications after surgeries for a variety of etiologies, including high-grade sarcoma, meningioma, hip replacement, and coronary artery bypass graft (Table 1). The clinical presentation was usually acute renal failure with heavy proteinuria and hematuria. Only three patients had low complement levels. In three patients (patients 1, 3, and 4), the infection was not suspected to be clinically associated with the glomerular disease; two of these patients were the diabetic patients with infected leg ulcers. During the study period, we identified 24 native kidney biopsies with primary IgA nephropathy and 3 adult native kidney biopsies with postinfectious GN, not related to staphylococcal infection. One biopsy revealed *S. aureus* endocarditis–related diffuse proliferative GN, but we did not include this in our study because *Staphylococcus* endocarditis–associated proliferative GN is a well-defined and recognized glomerular disease entity. During the study period, we were not aware of a native kidney biopsy in our material with changes related to *Staphylococcus* infection without glomerular IgA deposits.

Light microscopy revealed variable degrees of mesangial and intracapillary hypercellularity (Figure 1; Table 2). In four patients, hypercellularity was mild and localized primarily to the mesangium, with only mild segmental intracapillary hypercellularity. Prominent intracapillary hypercellularity was noted only in two patients, and, in both of them, hyalin thrombi, which resemble cryoglobulin, were observed in the glomerular capillaries (Figure 2). In one of these biopsies, the hyalin thrombi were quite prominent; in the other, one they were few. Rare hyalin thrombi were seen in an additional biopsy, but in this specimen only mild segmental intracapillary hypercellularity was present. Five of the eight patients had moderate to prominent interstitial fibrosis and tubular atrophy at the time of the biopsy. Only in three patients was the tubulointerstitial injury graded as mild.

IF revealed IgA predominant or codominant immune complex deposits in all cases (Table 3; Figures 3 and 4). However, the intensity of the IgA fluorescence was graded as strong in only one case (the biopsy with many hyalin thrombi). In the remaining biopsies, the IgA staining intensity was mild to

Table 1. Clinical characteristics of patients with *Staphylococcus* infection-associated glomerulonephritis[a]

Patient	Age/ Gender	*Staphylococcus*	Underlying Condition	Origin of Infection	Serum Creatinine at Biopsy	Proteinuria	Hematuria	Serum Complement	Follow-Up Time	Last Serum Creatinine
1	60/M	MRSA	Advanced diabetes	Cellulitis of leg	1.3 mg/dl	9 g/24 h	3 to 5 RBC/HPF	normal	6 mo	Dialysis
2	80/M	MRSA	High grade sarcoma	Scrotal abscess	6.0 mg/dl	2.5 g/24 h	gross	normal	13 mo	Dialysis
3	68/M	MRSA	CABG	Donor vessel site	4.2 mg/dl	>300 mg/dl	casts	normal	8 mo	Dialysis[b]
4	67/F	MRSA	Severe diabetes	Leg ulcer	9.5 mg/dl	>200 mg/dl	casts	C3: 69, C4: 30	6 mo	Dialysis
5	68/M	MRSE	Meningeoma	Line infection	4.2 mg/dl	>200 mg/dl	3 to 4 RBC/HPF	C3: 42, C4: 11	2 mo	0.9 mg/dl
6	56/F	MSSA	Epidural abscess	Endocarditis	3.2 mg/dl	349 mg/dl	10 to 14 RBC/HPF	C3: 84, C4: 7	2 mo	1.8 mg/dl
7	75/M	MSSA	MVA	Infected wound	3.4 mg/dl	>200 mg/dl	>50 RBC/HPF	normal	3 mo	Dialysis[c]
8	62/M	MRSA	CAD, Hip replacement	Infected wound	4.8 mg/dl	7.7 g/24 h	30 to 50 RBC/HPF	normal	3 mo	2.0 mg/dl

[a]Normal range: C3 80 to 178 mg/dl; C4 12 to 42 mg/dl. MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *S. epidermidis*; MSSA, methicillin-sensitive *S. aureus*; M, male; F, female; CAD, coronary artery disease; CABG, coronary artery bypass graft; MVA, motor vehicle accident.

[b]Patient's renal function temporarily improved.

[c]Patient's renal function improved but became repeatedly septic.

Table 2. Light microscopic and electron microscopic findings in the kidney biopsies of *Staphylococcus* infection-associated glomerulonephritis[a]

Patient	Glomeruli						Tubulointerstitium				Vasculature		Electron Microscopic Findings			
	# of Glomeruli	Sclerotic Glomeruli	Mesangial Hypercellularity	Intracapillary Hypercellularity	Crescents	Other	Inflammation	ATN	Fibrosis	Tubular Atrophy	Arteriolar Hyalinosis	Intimal Thickening	Mesangial Deposits	Glomerular Capillary Deposits	Large Subendothelial Deposits	Other
1	24	3	1+	0	0	3 + DGS	0.5+	1+	3+	3+	3+	2+	1+	1+	0	GBM thickening
2	18	1	1.5+	0.5+S	0		1+	2+	2+	2+	2+	2+	1+	0	0	
3	15	2	0.5	0	0		1+	1+	2+	2+	1+	1+	1+	0	0	
4	29	12	1+	0	0	3 + DGS	2+	1+	3+	3+	1+	1+	1+	1+	0	GBM thickening
5	8	3	3+	3+	0	Hyalin thrombi	1+	1+	1+	1+	3+	N/A	3+	3+	3+ (no substructure)	
6	18	0	3+	3+	0	Rare hyalin thrombi	1+	1+	1+	1+	1+	2+	2+	0.5	0	
7	16	2	0.5+	1 +S	0	Rare hyalin thrombi	1.5+	2+	2+	2+	2+	0	3+	0.5	0	
8	16	1	2+	1 +S	0		2+	2+	1+	1+	2+	N/A	1+	0.5+	0	

[a]Lesions are graded from 0 to 3+ (0: absent; 1+: mild, 2+: moderate, 3+: prominent). DGS, diabetic glomerulosclerosis; S, segmental; ATN, acute tubular necrosis; GBM, glomerular basement membrane; N/A, not applicable.

Figure 1. A glomerulus with mesangial hypercellularity and expansion from the biopsy of patient 2. Hematoxylin and eosin (H&E), magnification ×400.

moderate. The IgA fluorescence was localized mainly to the mesangium; some granular glomerular capillary staining was noted in three biopsies. Deposition of IgG was seen in four of the eight biopsies, and IgM was present in three biopsies. C3 deposits were seen in all but one biopsy; however, C1q and C4 were seen in only three cases. In one biopsy (patient 5), hyalin thrombi were present even in the frozen sections and these hyalin thrombi were strongly positive for IgA and IgG (Figure 4). Compared with the eight control idiopathic IgA nephropathy cases, the pattern of IF was not strikingly different in the *Staphylococcus* infection-related cases; however, the control

Figure 2. A glomerulus with intracapillary hypercellularity from the biopsy of patient 5. Note the intracapillary hyalin thrombus at approximately 2 o'clock. Periodic acid Schiff (PAS), magnification ×1000.

Table 3. Immunofluorescence findings[a]

Patients	IgG	IgA	IgA1	IgA2	C3	C4	C1q	IgM	Fibr	Kappa	Lambda
1	2 + m. s	2 + m	0.5 to 1 + m	0.5 + m	0	0.5 to 1 + s	0.5 + m. s	0.5 to 3 + s	0	1 + m	2 + m
2	0	1 + m	1 + m	0.5 + m	2 + m	0	0	0	1 + s	0.5 + m	2 + m
3	0	2 + m/c	2 + m	1 + m	1 to 2 + m	0	0	0	1+	1 + m	2 + m
4	0	1 to 2 + m	1 + m. s	1 + m	1 to 2 + m	0	2+	0.5 to 3 + s	1 + s	0.5 + m	1 + m
5	3 + m/c	3 + m/c	2 to 3 + m	1 to 2 + m	3 + m/c s	1 + s	2+	0	0	2 to 3 + m/c s	3 + m/c s
6	1 + m. s	1 + m/c s	0.5 to 1 + m	0.5 + m	1 to 2 + m	0	0	1 + m	1 + m	1 + m	1 to 2 + m
7	0.5 + m	1 to 2 + m	0.5 to 1 + m	0.5 + m	3 + m/c s	0	0	0	1 + s	0.5 + m	1 to 2 + m
8	0	1 + m	0.5 + m	0.5 m/c s	2 to 3 + m	0	0	0	0	0	0.5 + m. s
Controls											
1	2 + m	3 + m	3 + m	2 to 3 + m	3 + m	0	0	0	0	2 + m	3 + m
2	0	2 + m	2 + m	2 + m	1 to 2 + m	0	0	0.5 + m	2+	1 to 2 + m	2 + m
3	0	3 + m	3 + m. s	2 + m	0.5 + m	0	0	0.5 + m	0.5 +	2 + m	3 + m
4	0	2 + m	2 + m	2 + m	2 + m	0	0	0	1 to 2 + s	1 to 2 + m	2 + m
5	0	3 + m	3 + m	3 + m	2 to 3 + m	0.5 + s	0	0.5 + m	0	3 + m	2 to 3 + m
6	1 + m	2 to 3 + m	1 to 2 + m	1 + m	0.5 + m	0	0	1 + m	0	1 + m	1 to 2 + m
7	0	3 + m	3 + m	2 to 3 + m	3 + m	0	0	0	2 + s	2 to 3 + m	3 + m
8	0	2 to 3 + m	2 + m	2 + m	0.5 + m	0	0	0.5 + m	2 + m	2 to 3 + m	2 + m

[a]m, mesangial; c, glomerular capillary; s, segmental; Fibr, fibrinogen. Intensity of staining: 0, absent; 1+, mild; 2+, moderate; 3+, prominent.

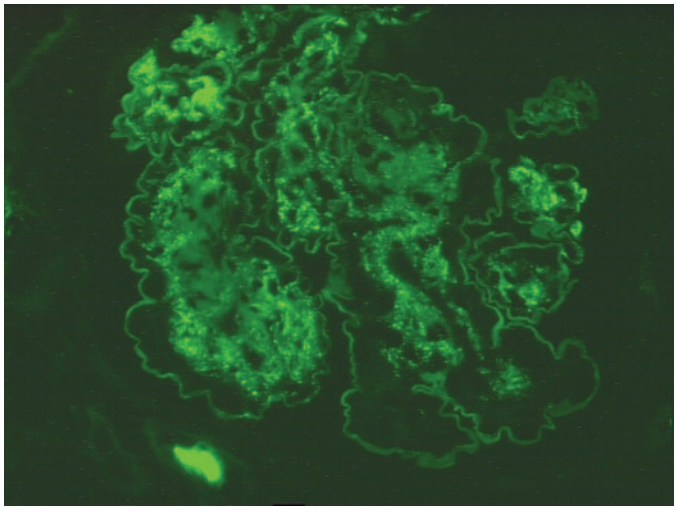

Figure 3. Direct immunofluorescence showing granular mesangial staining for IgA in the expanded mesangium of the biopsy of patient 4, who had underlying diabetic glomerulosclerosis. The IgA fluorescence was not strong in most cases. Magnification ×400.

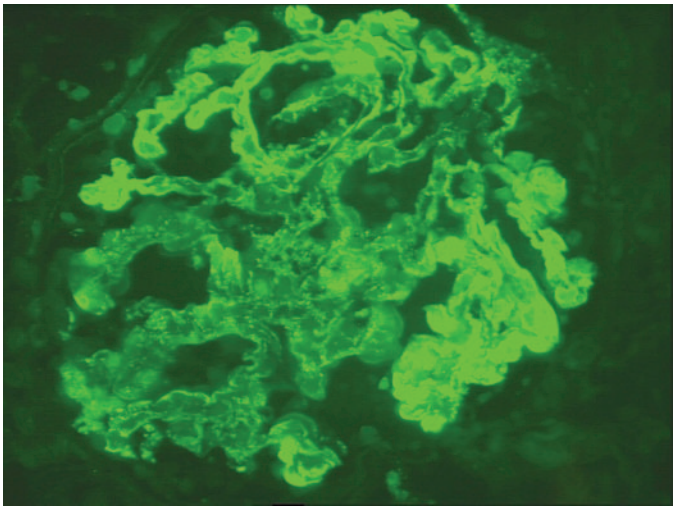

Figure 4. Strong fluorescence for IgA1 in the biopsy of patient 5, who had large, cryoglobulin-like subendothelial deposits. Magnification, ×400.

cases showed more intense mesangial IgA deposits. Glomerular capillary deposits were not seen (Table 3). Interestingly, we detected both IgA1 and IgA2 in the *Staphylococcus* infection-related GN cases as well as in the control primary IgA nephropathy cases. Although the IgA1 fluorescence was usually stronger, this somewhat contradicts data in the literature (15). The IgA2 staining in our cases may be explained by the antibody we used or by the indirect IF methodology applied, which is more sensitive than the routinely used direct IF.

Ultrastructural examination revealed variable numbers of mesangial electron-dense deposits in all cases and scattered glomerular capillary deposits in six cases (Table 2; Figure 5). These glomerular capillary deposits were usually small, mainly intramembranous, and rarely subepithelial. Obvious subendothelial deposits were only noted in the biopsy of patient 5. These subendothelial deposits were very large, but did not have the characteristic microtubular substructure of cryoglobulin. However, it is important to note that these deposits most likely represent IgA/IgG mixed cryoglobulin deposits, which may not have the substructure of IgG/IgM mixed cryoglobulins. None of the biopsies had large subepithelial deposits (humps), which are usually seen in postinfectious GN.

Treatment involved a variety of antibiotics, depending on antibiotic resistance pattern. Only one patient (patient 6) received a short course of steroid with no improvement. Although our follow-up time is short, the renal outcome appears to be poor. This can be best explained by the fact that many patients had severe underlying conditions. Interestingly, the three patients who recovered renal function (patients 5, 6, and 8) had only mild interstitial fibrosis and tubular atrophy. All patients with moderate or prominent interstitial fibrosis are

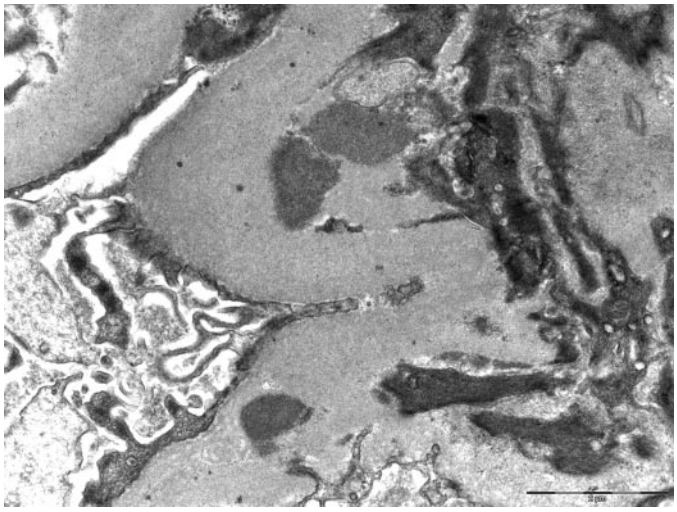

Figure 5. Paramesangial and intramembranous electron-dense immune-type deposits in the biopsy of patient 1, who also had underlying diabetic glomerulosclerosis. Uranyl acetate lead citrate; original magnification, ×12,000.

currently on dialysis. One patient (patient 7) temporarily showed improvement of renal function, but unfortunately became repeatedly septic and needed to be dialyzed.

Discussion

Because the prevalence of IgA nephropathy is high in Japan and other Asian countries, particularly compared with the prevalence in the US population, one could argue that *Staphylococcus* infection-related IgA predominant GN is primarily an Asian association. Our experience, however, suggests otherwise. This study demonstrates that *Staphylococcus* (especially MRSA) infection-associated GN occurs prominently in the US. Furthermore, as the incidence of MRSA infection increases globally, the incidence of MRSA-associated GN likely will also increase. Our findings and data in the literature indicate that these patients usually present with acute renal failure, active sediment, and frequently heavy proteinuria, and the renal biopsy reveals IgA-codominant or -predominant glomerular immune complex deposits (2,4,7,8). Because of the IF findings, it is possible that some of these cases are misdiagnosed as idiopathic IgA nephropathy. Some patients may develop purpuric skin lesions, which resemble Henoch Schönlein purpura. It is important not to treat these patients with immunosuppressive medication. Therefore, establishing the correct diagnosis is quite relevant. The diagnosis of MRSA-associated GN cannot be made based on renal biopsy findings alone. Clinical history of infection is required, but sometimes the *Staphylococcus* infection may not present as an overt sepsis. Recognition of the disease is not always easy, particularly in diabetic patients with leg ulcers, where the association of the renal disease and the leg ulcer may be overlooked. A comparison of clinical findings in *Staphylococcus* infection-associated GN and idiopathic (primary) IgA nephropathy is provided in Table 4. A summary of previously published cases, for which relevant clinical and morphologic data were available, is displayed in Table 5.

The morphologic findings in cases of *Staphylococcus* infection-associated GN are clearly more similar to those found with IgA nephropathy/Henoch Schönlein purpura than to those found with other postinfectious glomerulonephritides, including poststreptococcal GN. Although diffuse intracapillary proliferative GN was noted in two of our patients (patients 5 and 6), these patients also had cryoglobulinemia and the glomerular

Table 4. Comparison of clinical characteristics of *Staphylococcus* infection-associated glomerulonephritis and idiopathic IgA nephropathy[a]

Patient Characteristic	*Staphylococcus* Infection-Associated GN[b]	Idiopathic IgA Nephropathy
Age at peak incidence	50 to 89 yr	20 to 30 yr
Sex	80 to 90% males	About 70% male
Race	Most reported in Japanese population, but seen in whites, and Hispanics	Highest incidence in Asians, low incidence in blacks
Association with infection	Usually present	Occasional history of infection, (30 to 40%)
Microbes	*Staphylococcus*, about 70% MRSA	Viral or bacterial
Site of infection	Visceral abscess, postoperative infections, skin infection, infected leg ulcers in diabetic patients	URTI[c]
Onset of GN after infection	5 to 10 wk after *Staphylococcal* infection, even up to 16 wk	1 to 2 days after URTI, or may accompany infection, 'synpharyngitic' hematuria
Gross hematuria at presentation	50 to 60% of cases	30 to 40% of cases; often recurrent
Proteinuria	Heavy, frequently nephrotic range	Mild, unless significantly progressed glomerular disease
Serum complement	May be low (30% of patients), or low normal	Normal
Cryoglobulins	May be present	Usually absent
Acute renal failure	Common	Uncommon
Treatment	Antibiotics	Steroids/immunosuppressive drugs for those with active or progressive disease

[a]Based on our own observations and data in the literature.
[b]GN, glomerulonephritis.
[c]URTI, upper respiratory tract infection.

Table 5. Summary of clinical and morphologic features in published cases of *Staphylococcus* infection-associated glomerulonephritis

	Previous Reports	*n*	Age group (yr)	*Staphylococcus*	Origin of Infection	Latent Period (wk)	Clinical Presentation	Serum Complement	Glomerular Histology	IgA Deposits on IF	Treatment	Outcome
1	Koyama A, *et al.* (2)	10	21 to 84; 8 pts >50	MRSA	Abdominal abscess, pneumonia, empyema, septicemia	2 to 16 wk	RPGN with nephrotic syndrome, few with purpura	Normal	Mesangial proliferative GN, diffuse proliferative GN, with crescents	Co-dominant, mesangial, capillary loops	Vancomycin	7 of 10 pts improved; 3 pts died
2	Yoh K, *et al.* (4)	1	71	MRSA	Pneumonia after cancer surgery	1 wk	Subnephrotic proteinuria, microscopic hematuria	Normal	Mild to moderate mesangial proliferation	Co-dominant, mainly capillary loops	Imipenem, cilastatin	Recovered
3	Nagaba Y, *et al.* (8)	8	23 to 75; 6 pts >50	MRSA	Pneumonia, visceral abscess	4 to 16	RPGN, purpura, heavy proteinuria,	Low normal	4 of 8 pts crescentic, 4 of 8 pts mild to moderate mesangial proliferation	Dominant, mesangial	5 of 8 pts vancomycin, 1 of 8 pts minocycline + ofloxacin, 2 pts steroids	Death in 2 pts treated with steroids; others recovered
4	Handa T, *et al.* (6)	1	57	MSSA	Infected dermatitis lesions	0	Nephrotic syndrome, microscopic hematuria	Low normal	Diffuse proliferative GN	Dominant, mesangial, capillary loops	Cefdinir, cefazolin, prednisone	Recovered
5	Spector DA, *et al.* (10)	3	30 to 80	SA	Empyema, subcutaneous abscesses, septicemia	0 to 6 wk	RPGN, nephrotic range proteinuria in 2 pts, subnephrotic in 1 pt	Normal	Moderate mesangial proliferative GN, diffuse proliferative GN	Co-dominant mesangial, 1 pt capillary loops	Methicillin	2 pts recovered, 1 pt died
6	Griffin MD, *et al.* (11)	1	72	SA	Postsurgical sternal wound infection	1 wk	ARF, microscopic hematuria	Low normal	Mesangial proliferative GN	Co-dominant mesangial, glomerular capillary loops	Vancomycin	Recovered
7	Pola E, *et al.* (12)	1	30	SA	Arthroscopy knee surgery (septic arthritis)	Several days	ARF, subnephrotic proteinuria, microscopic hematuria	Not stated	Mild mesangial proliferative GN	Dominant mesangial	Ciprofloxacin, methyl-prednisolone, prednisone	Recovered
8	Nasr SH, *et al.* (14)	5	50 to 89; 4 pts >50	MSSA, SE	Infected foot ulcers, rectal abscess	2 to 12 wk	ARF, subnephrotic proteinuria, microscopic hematuria	Low	Diffuse proliferative GN,	Dominant, mesangial, few"humps" in capillary loops	Antibiotics, not specified	1 pt recovered, others on dialysis
9	our data	8	50 to 80	MRSA, MSSA, MRSE	Leg ulcers, infected wound, line infection	0 Weeks	RPGN, ARF, nephrotic syndrome, hematuria	Normal in 5 pts, low in 3 pts	5 mesangial proliferative pts, 3 diffuse proliferative with hyalin thrombi pts	Predominant or co-dominant	Vancomycin	3 pts recovered, 5 pts on dialysis

SA, *S. aureus* (antibiotic sensitivity not specified); SE, *S. epidermidis* (antibiotic sensitivity not specified); RPGN, rapidly progressive glomerulonephritis; ARF, acute renal failure; pt(s), patient(s).

intracapillary hypercellularity may have been related to that. In the remaining cases, intracapillary inflammatory cells, including polymorphonuclears, were sparse, which is in contrast to the five patients reported by Nasr *et al.* (14). Although intracapillary proliferative GN secondary to *Staphylococcus* infection was reported in several series, many patients described in the literature had primarily or purely mesangial proliferative GN without apparent intracapillary hypercellularity (2,4,8,10–12). It is worth noting that all patients described by Nasr *et al.* (14) had underlying diabetic nephropathy. It is possible that diabetic patients mount a somewhat altered immune response to bacterial antigens, which may explain the difference in the glomerular inflammatory response. Local glomerular microenvironmental factors in diabetic glomerulosclerosis may also contribute to the differences in the degree of glomerular inflammatory response. Large subepithelial humps were not evident in any of our cases and were only rarely seen in the patients reported in the literature. Even the diabetic patients of Nasr *et al.* (14) had only rare subepithelial deposits, and only some of them were hump-shaped. Crescents may occur in some patients (2,3), but they are uncommon and they were not seen in any of our biopsies. In our experience, if a kidney biopsy reveals mesangial IgA deposits associated with acute tubular necrosis, some degree of interstitial inflammation, and a large number of red blood cells in the tubules, and if the patients clinically present with acute renal failure or rapidly progressing GN, the possibility of an underlying *Staphylococcus* infection should be considered.

The association of *Staphylococcus* infection and the renal disease may be established only after renal biopsy and a specific inquiry about possible staphylococcal infection in these patients, as seen in three of our cases. The infection may not be always clinically obvious and may be overlooked by the nephrologist (*e.g.*, not inquiring about the exact pathogen in a diabetic patient with renal disease and infected leg ulcer). The *Staphylococcus* infection can be coexistent with the renal disease, or the renal disease may follow the infection with a latency and may manifest only when the blood cultures turn negative (Table 5). However, it can be quite difficult to exactly establish the temporal relationship between the staphylococcal infection and renal disease. The infection may have started earlier than diagnosed, or, on the other hand, a negative blood culture would not exclude a latent, persistent infection, as indicated by the few recurrent cases.

Interestingly, it appears that sometimes the *Staphylococcus* infection is associated with cryoglobulinemia. In one of these biopsies, we could prove that the large glomerular intracapillary cryoglobulin-like immune complexes contained IgA and IgG; therefore, the role of IgA/IgG containing mixed cryoglobulins emerge. In fact, this patient tested positive for circulating cryoglobulins. Unfortunately, we were unable to obtain data on the exact composition of the cryoglobulins in the blood. Cryoglobulinemia may be responsible for the more prominent glomerular intracapillary hypercellularity in these cases.

Our patients and those in the literature (2,4,6–8,13) indicate that the outcome is quite variable. Recovery of renal function after antibiotic treatment may occur (2,6,8). Obviously, steroid treatment should be avoided. This is important to emphasize because high-dose steroid therapy is often recommended for severe, rapidly advanced idiopathic IgA nephropathy. Although occasional case reports advocate the use of steroids in GN associated with infective endocarditis (16), we are unaware of any credible source that recommends using immunosuppression for GN associated with active bacterial infection, because the infection can drastically worsen (17). Indeed, our own reported experience with immunosuppressive therapy in patients with GN due to active bacterial infection is quite negative. The patient's underlying condition is probably quite important in the outcome of the disease. Four of the five patients reported by Nasr (14) developed end-stage renal disease, but all of their patients had quite prominent underlying diabetic nephropathy and a long history of diabetes mellitus with a variety of complications. We would like to emphasize that *Staphylococcus* infection-related IgA-predominant GN may also develop in nondiabetic patients with *Staphylococcus* infection. Interestingly, our data indicate that an important predictor of potentially good outcome is the absence of significant chronic injury in the renal parenchyma. Five of eight patients in our series had moderate or prominent chronic tubulointerstitial injury and all of them needed continuous dialysis treatment. Only the three patients who had mild chronic tubulointerstitial disease recovered renal function. Therefore, careful evaluation of the renal biopsy for the degree of chronic injury is relevant to determine potential outcome of the disease. Although five of our eight patients had MRSA infection, it appears evident that other *Staphylococcus* infections may also be associated with IgA containing glomerular immune complex deposits.

Unfortunately, a number of questions remain unanswered. One might argue that these patients may incidentally have preexisting IgA deposits, which are only discovered because of the superimposed *Staphylococcus* infection-related renal disease. In our opinion, it is highly unlikely that so many patients with *Staphylococcus* infection and renal disease (GN) have coincidental glomerular IgA deposits. Also, the presence of IgA containing cryoglobulins in one patient (this patient later recovered renal function) strongly suggests the pathogenic role of IgA containing immune complex deposits in these patients. We cannot answer the question as to whether these IgA containing glomerular immune complex deposits persist or disappear after the *Staphylococcus* infection has been eradicated. The fact that the patient with the abundant cryoglobulin-like IgA containing deposits recovered renal function indicates that, at least to some degree, this immune complex deposition is reversible. Unfortunately, no follow-up biopsies are available.

The pathogenesis of *Staphylococcus* infection-related GN is not entirely clear. Koyoma and coworkers (2,9) indicate the role of *Staphylococcus* superantigens in the pathogenesis. Staphylococcal enterotoxins may behave as superantigens that can bind directly to major histocompatibility complex (MHC) class II molecules on antigen-presenting cells. The enterotoxin/MHC class II complex then binds to the T cell receptor Vβ region without MHC restriction. Koyama *et al.* propose that these processes results in massive T cell activation with subsequent cytokine burst. The cytokines activate B cells that will produce

polyclonal IgA and IgG, which would eventually result in immune complex formation. Recently, Koyoma *et al.* proposed a particular *S. aureus* cell envelope antigen as the pathogenetic protein (9). They were able to co-localize the antigen with the glomerular IgA deposits in the glomeruli of affected patients. Also, the same group recently developed an experimental model in Balb/c mice after immunization of the animals with this *S. aureus* wall antigen (18,19). The animals developed mesangial IgA deposits.

In summary, in this publication we emphasize the potential role of staphylococci in the induction of GN with IgA codominant or predominant glomerular immune complex deposits. With the increasing prevalence of staphylococcal (in particular MRSA) infections, this particular GN should be kept in mind if patients have unusually severe renal symptoms, including renal failure, hematuria, and severe proteinuria with the biopsy findings of mesangial IgA containing immune complexes. In such instances, the possibility of underlying staphylococcal infection should be considered. Making the correct diagnosis is imperative to avoid immunosuppressive treatment of a GN that is associated with staphylococcal infection.

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