

Staphylococcal Infection–Related Glomerulonephritis With Cryoglobulinemic Features



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Introduction: Staphylococcal infection–related glomerulonephritis (GN) has been shown to represent a unique form of infection-related GN that contains IgA-dominant deposits and is often seen concurrently with the bacterial infection. Biopsies commonly reveal an endocapillary proliferative and/or exudative or mesangial proliferative GN. Rare cases have been reported to show cryoglobulin-like features, including hyaline pseudothrombi and wireloop deposits; however, detailed characterization of these cases is lacking.

Methods: The pathology archives from the University of Utah and Sharp Memorial Hospital were reviewed from January 2016 to September 2017 in search of cases with GN containing IgA-dominant deposits and features of cryoglobulinemia.

Results: Of 1965 native kidney biopsies, 5 showed IgA-dominant GN with cryoglobulinemic features. All patients had active staphylococcal infections at the time of biopsy. All presented with acute kidney injury (serum creatinine range: 1.7–6 mg/dl), and all had proteinuria and hematuria. All biopsies showed exudative GN, and 4 biopsies had focal crescents. All had focally prominent hyaline pseudothrombi with or without wireloop deposits, and all showed co-dominant staining for IgA and C3 on immunofluorescence microscopy. Serologic testing for cryoglobulinemia was performed in 3 patients and was transiently positive in 1 patient. Four patients required hemodialysis at last follow-up, whereas 1 patient returned to baseline kidney function.

Conclusion: IgA-dominant GN with cryoglobulinemic features is an uncommon but severe form of glomerular injury in patients with staphylococcal infections. Four of 5 patients had crescentic glomerular injuries, all of whom required hemodialysis at last follow-up. Patients with IgA-dominant GN with features of cryoglobulinemia should be evaluated for active staphylococcal infection.

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KEYWORDS: acute kidney injury; cryoglobulinemia; infection-related glomerulonephritis

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GN related to bacterial infection has long been recognized as a form of kidney injury, with early descriptions of post-streptococcal GN dating back to the 19th century.¹ Although post-streptococcal disease has represented the prototypical example of bacterial infection-related GN, the past 2 decades have seen an epidemiological shift in the underlying cause, morphologic features, and therapeutic regimens for this collection of diseases.² In developed countries, staphylococcal species have emerged as common etiologic

agents in cases of bacterial infection-related GN (IRGN) and are associated with distinct morphologic features and clinical implications that differ from classic postinfectious GN. GN associated with staphylococcal infection shows deposits that stain in a dominant or co-dominant fashion for IgA and the C3 component of complement by immunofluorescence microscopy and clinically occurs in the setting of an active infection.

During the last decade, an increasing body of literature has been amassed regarding the morphologic and clinical features of staphylococcal IRGN. Although diffuse proliferative and exudative GN is the most commonly encountered pattern of glomerular injury, less common injuries including GN with cryoglobulinemic features have been rarely reported.^{3,4} We present a clinicopathologic series of 5 patients

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with cryoglobulin-like GN with IgA-dominant deposits, all of whom had an active *Staphylococcus aureus* (*S. aureus*) infection at the time of biopsy.

MATERIALS AND METHODS

The pathology archives from the University of Utah (Salt Lake City, UT) and Sharp Memorial Hospital (San Diego, CA) were searched from January 2016 to September 2017. All cases were processed for standard light, immunofluorescence, and electron microscopy. Cases that showed GN with IgA-dominant deposits were reviewed for descriptions of cryoglobulinemic features, such as hyaline pseudothrombi and wireloop deposits. Hyaline pseudothrombi were defined as intracapillary plugs within glomeruli that were eosinophilic on hematoxylin and eosin stain and stained strongly on periodic acid Schiff, with pale to negative staining on the Jones methenamine silver stain. Other features included a homogenous appearance of the intracapillary plug and a cleft between the intraluminal material and capillary basement membrane. Wireloop deposits were defined as segmental band-like hyaline thickening of capillary loops with a staining pattern similar to that described for hyaline pseudothrombi. After identification of cases of IgA-dominant GN with cryoglobulinemic features, pathologic and clinical data were reviewed, as was clinical follow-up, when available.

Reviewed clinical features included presence of an underlying infection, serologic studies (including cryoglobulin studies, viral and/or autoimmune serologic studies, and presence of a paraprotein), presence of proteinuria and/or hematuria, and renal function. Nephrotic-range proteinuria was defined as 3.5 g of protein per day or a spot urine protein-to-creatinine ratio of 3.5 g/g.

RESULTS

Biopsy Selection

During the study period, 1965 native kidney biopsies were reviewed, 258 (13%) of which showed immune complex deposition with IgA-dominant staining by immunofluorescence microscopy. Of the biopsies with IgA-dominant deposits, 5 showed hyaline pseudothrombi with or without wireloop deposits on light

microscopy. These 5 biopsies represented 0.25% of all native kidney biopsies during the study period and 1.9% of biopsies with IgA-dominant deposits.

Clinical Features at Presentation

All 5 patients with IgA-dominant deposits and cryoglobulinemic features had active bacterial infections with *S aureus* at the time of biopsy. Clinical characteristics of these patients are detailed in Table 1. Three patients were men, and 4 were older than 60 years of age. All 5 patients presented with acute kidney injury (serum creatinine range: 1.7–6 mg/dl), 1 of whom was anuric (patient #3). Proteinuria and hematuria was present in all 4 patients making urine. Degree of proteinuria was quantified in 2 patients and was in the nephrotic range in 1 patient (patient #2). Three patients required hemodialysis at presentation (patients #1, 3, and 5). Patient #5 had underlying diabetes mellitus, and patient #4 had a history of rheumatoid arthritis being treated with methotrexate. Two patients (patients #3 and 5) had leg ulcers as the primary site of infection. Two patients had deep seated infections, including 1 patient with vertebral osteomyelitis (patient #2) and 1 patient with an epidural abscess adjacent to the lumbar spine (patient #4). Patient #1 presented with bullous impetigo. Three patients (patients #2, 4, and 5) had bacteremia. Bacterial cultures were available for 4 patients, all of which grew methicillin-susceptible *S aureus* (MSSA). The patient with bullous impetigo was presumed to have a *S aureus* infection. Serologic testing for cryoglobulins was performed in 3 patients and was initially positive in patient #3 with cryoprecipitate composed of IgA (4 mg/dl; reference: 0 mg/dl), IgG (4 mg/dl; reference: 0 mg/dl), and IgM (5 mg/dl; reference: 0 mg/dl). Serum protein electrophoresis (SPEP) with immunofixation electrophoresis concurrent with the positive cryoglobulin assay was suggestive of monotypic IgA- λ ; however, repeat testing upon hospital transfer was negative for both cryoglobulins and paraprotein. SPEP was performed on 3 additional patients (patients #2, 4, and 5), all of whom showed a polyclonal increase in IgA without monoclonal proteins. Complement C3 levels were low to borderline low in all 4 patients with

Table 1. Clinical features

Patient	Age (yr)/sex	Infection	Cryoglobulin	HCV	C3 (mg/dl)	Presenting SCr (mg/dl)	Treatment	Follow-up time (mo)	Outcome
#1	33/F	Bullous impetigo	Negative	Negative	N/A	3.7	Antibiotic + CS	1	HD
#2	62/M	MSSA/osteomyelitis, bacteremia	Negative	Positive	83	4.3	Antibiotic + CS	3	HD
#3	75/M	MSSA/foot ulcer	Positive	Negative	41	4	Antibiotic	9	HD
#4	63/F	MSSA/epidural abscess, bacteremia	N/A	Negative	60	1.7	Antibiotic	2	SCr: 0.75 mg/dl
#5	61/M	MSSA/diabetic foot, bacteremia	N/A	N/A	85	6	Antibiotic	6	HD/Expired

CS, corticosteroids; HCV, hepatitis C virus; HD, hemodialysis; MSSA, methicillin-susceptible *Staphylococcus aureus*; SCr, serum creatinine.

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