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Update on endocarditis-associated glomerulonephritis

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Glomerulonephritis (GN) due to infective endocarditis (IE) is well documented, but most available data are based on old autopsy series. To update information, we now present the largest biopsy-based clinicopathologic series on IE-associated GN. The study group included 49 patients (male-to-female ratio of 3.5:1) with a mean age of 48 years. The most common presenting feature was acute kidney injury. Over half of the patients had no known prior cardiac abnormality. However, the most common comorbidities were cardiac valve disease (30%), intravenous drug use (29%), hepatitis C (20%), and diabetes (18%). The cardiac valve infected was tricuspid in 43%, mitral in 33%, and aortic in 29% of patients. The two most common infective bacteria were *Staphylococcus* (53%) and *Streptococcus* (23%). Hypocomplementemia was found in 56% of patients tested and ANCA antibody in 28%. The most common biopsy finding was necrotizing and crescentic GN (53%), followed by endocapillary proliferative GN (37%). C3 deposition was prominent in all cases, whereas IgG deposition was seen in <30% of cases. Most patients had immune deposits detectable by electron microscopy. Thus, IE-associated GN most commonly presents with AKI and complicates staphylococcal tricuspid valve infection. Contrary to infection-associated glomerulonephritis in general, the most common pattern of glomerular injury in IE-associated glomerulonephritis was necrotizing and crescentic glomerulonephritis.

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Renal disease due to infective endocarditis (IE) is well established, with the earliest reports of glomerular lesions published over 100 years ago.^{1–3} Although initially believed to be primarily embolic,^{1–3} it later became clear that over 80% of cases represented focal, segmental, or diffuse proliferative glomerulonephritis (GN) with prominent endocapillary proliferation and occasional infiltrating leukocytes.^{4–6} However, the literature describing nephritis associated with IE still relies heavily on autopsy studies conducted in the pre- and early postantibiotic era or small renal biopsy studies from the 1970s.

Several reviews have emphasized the evolution occurring in recent decades in renal complications of infectious diseases in general, with particular emphasis on the change in demographics from younger to older patients, the frequency of comorbidities such as diabetes and HIV, and the change in predominance of infectious agents from primarily streptococcal to a broader array of organisms with predominance of *Staphylococci*.^{7–10}

IE occurs in 30 to 60% of patients with *Staphylococcus aureus* bacteremia and carries a mortality rate of 40–50%.¹¹ Over the past decades, IE outcomes have not improved, and infection rates are steadily increasing.¹¹ Recent case series and reviews of IE have compared findings from current and previous eras, confirmed similar changes in the demographics of the disease, and updated the clinical and pathologic features in both adults and children.^{5,12} However, few of these recent reports have focused primarily on IE-related renal lesions, and much of the data currently available still include predominately autopsy-derived information.^{5,13}

Based on all of the above, we investigated the clinicopathologic characteristics of a large cohort of patients with IE-associated GN diagnosed by kidney biopsy between 2001 and 2011 in two large nephropathology laboratories. Our data indicate that IE-associated GN in the new era has significantly different clinical and pathologic changes from those described historically.

RESULTS

Clinical features

The clinical characteristics of 49 patients undergoing a renal biopsy with documented IE are detailed in Table 1. Features of note include a male predominance (3.5:1) with a mean age

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Table 1 | Demographics and clinical characteristics

Gender/age	
Male:female, n/n (%/%)	38/11 (78/22)
Age (years), mean (range)	48 (3-84)
	n (%)
Clinical syndrome n = 47 with data (%)	
Acute renal failure	37 (79)
Acute nephritic syndrome	4 (9)
Rapidly progressive glomerulonephritis	3 (6)
Nephrotic syndrome	3 (6)
Predisposing states^a	
Intravenous drug abuse	14 (29)
Prosthetic cardiac valve	9 (18)
Cardiac valve disease/Intracardiac shunt	6 (12)
Associated conditions	
Hepatitis C	10 (20)
Diabetes mellitus	9 (18)
Coronary artery disease	3 (6)
Chronic obstructive pulmonary disease	2 (4)
Congestive heart failure	1 (2)
Systemic lupus erythematosus	1 (2)
Recent surgery	1 (2)
Prostate cancer	1 (2)
	Median (range)
Laboratory data	
Serum creatinine at biopsy (mg/dl), n = 45	3.8 (1.0-12.0)
Proteinuria (g per day), n = 18	1.8 (0.5-15)
	n (%)
Hematuria, n = 37	36 (97)
ANA, n = 26	
Positive	4 (15)
ANCA, n = 29 ^b	
Positive	8 (28)
C3/C4, n = 32	
Low C3 only	12 (37)
Low C4 only	1 (3)
Low C3 and C4	5 (16)
Normal C3 and C4	14 (44)

Abbreviations: ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; C3, complement component 3; C4, complement component.

^aOne patient with a prosthetic valve and one patient with tricuspid insufficiency were also intravenous drug users.

^bANCA data was obtained in 43/49 patients (88%), although testing was only carried out in 29/43 patients.

at biopsy of 48 years. Two patients (4%) were children <18 years, and 30% of patients were elderly (≥60 years of age). Acute renal failure was the most common presenting condition (79%), with hematuria present in almost all cases (97%), yet typical acute nephritic syndrome in only <10% of cases. Conditions favoring endocarditis were noted in 29 patients including intravenous drug use (29%), prosthetic valves (18%), and prior valvular disease (12%). However, over 50% of patients did not have known prior cardiac disease. Associated comorbid conditions were noted in a minority of patients, the most common being hepatitis C infection (20%) and diabetes mellitus (18%) (Table 1).

Serologic studies

Serologic studies are summarized in Table 1. While 53% of the 32 patients tested for serum complement had reduced C3 (complement component 3) levels only a minority of patients (19%) in whom it was tested had reductions in C4, suggesting that most had activation of the alternative complement pathway. Anti-neutrophil cytoplasmic antibody (ANCA) data was obtained in 43/49 patients (88%), although testing was not carried out in 14/43 patients. Of the 29/43 patients with ANCA serologies drawn, 21 were negative (72%) and 8 were positive (28%). ANCA specificities of these 8 patients include 3 pANCA (one with positive MPO), 3 cANCA (two with positive PR3), 1 positive ANCA of unspecified type, and 1 with dual-positive MPO and PR3. Anti-nuclear antibody (ANA) was positive in 4/26 patients tested (15%). One patient with a positive ANA had history of systemic lupus erythematosus (SLE), although renal biopsy was without significant immune complex (IC) deposition. In the other three patients, the positive ANA was an isolated finding, with none having clinical evidence of SLE.

Cardiac involvement

Details of the IE are shown in Table 2. Cardiac infections most commonly involved the tricuspid valve (43%), followed by the mitral (33%), aortic (29%), and pulmonic (5%) valves. Five patients (12%) had involvement of two cardiac valves. One patient with tricuspid valve endocarditis also had a ventricular atrial shunt infection. Echocardiogram vegetations were noted in greater than two-thirds of patients. The most commonly noted sign of cardiac involvement in patients without vegetations on echocardiogram was new valvular regurgitation/murmur; the most common other criteria for diagnosis of IE in these patients included fever, septic pulmonary emboli, and predisposing heart condition or injection drug use. The most common vascular phenomena in the entire cohort was septic pulmonary infarcts, with only a minority of patients with intracranial hemorrhage, and rare patients with conjunctival hemorrhages, nail splinter hemorrhages, or evidence of mycotic aneurysm.

Infectious agents

The most common infectious agent found on blood culture was *S. aureus* (53%), with methicillin resistance in 56% (Table 2). *Streptococcus* species were the second most common pathogens found (23%). Less common causes of endocarditis were *Bartonella henselae* in four patients, *Coxiella burnetii* in two, *Cardiobacterium hominis* in one, and *Gemella* species in one. Four patients (9%) had culture-negative endocarditis, similar to findings in other series.^{14,15} Staphylococcal infection was the most common cause of endocarditis in patients with a history of intravenous drug abuse (77%), with the tricuspid valve or tricuspid and pulmonic valves (in one patient) affected in 83% and mitral or aortic valves in 17%. There were no significant associations noted between individual bacteria and the light microscopic appearance of GN, except that 6/7 cases with

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