RENAL LOCALIZATION OF THE MEMBRANE ATTACK COMPLEX IN SYSTEMIC LUPUS ERYTHEMATOSUS NEPHRITIS*

By GREGORY BIESECKER, SHEILA KATZ, AND DAVID KOFFLER‡

From the Department of Pathology and Laboratory Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania 19102, and The Rockefeller University, New York 10021

Immune complexes localized in the kidneys of patients with systemic lupus erythematosus (SLE)[1] appear to play a central role in the pathogenesis of glomerulonephritis. Evidence supporting this hypothesis has been obtained from serial serologic studies (1–3), assay of specific antigen-antibody systems (4–7), measurement of serum immune complex levels (8–11), and immunocytochemical examination of tissues from patients with SLE (12–14). Following tissue deposition of antigen-antibody complexes, the classical complement pathway may be activated *in situ*, generating complement fragments and effecting the release of cellular mediators (15). Chemotaxis, vasodilation, enhanced phagocytosis, initiation of coagulation, and local tissue damage may ensue following complement activation (16). The effector mechanisms by which complement-dependent immune complexes induce injury to cells and membranes in vivo remain to be clarified. Proteolytic enzymes derived from neutrophils and serum, lymphokines, high molecular weight kininogen-kallikrein-Hageman factor coagulation pathways, and the terminal complement complex have been implicated as mediators of cytotoxicity on the basis of in vitro studies (17).

To assess the role of the terminal complement complex in the inflammatory response, the tissue distribution of the membrane attack complex (MAC) comprised of C5b, C6, C7, C8, and C9, was investigated in kidneys manifesting SLE nephritis. In vitro studies have demonstrated that insertion of the MAC into the phospholipid bilayer of erythrocytes results in disruption of the membrane and cell lysis (18). In addition, the MAC has been observed on the surface membranes of neutrophils obtained from patients with SLE (19), although the pathogenetic significance of this phenomenon has not been determined. In this study the MAC was demonstrated in both glomeruli and in the region of peritubular basement membranes of kidneys with morphologic evidence of SLE nephritis. These findings suggest that the MAC interacts with sites on renal basement membranes and functions in vivo as a direct mediator of nephrotoxicity.

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‡ To whom reprint requests should be addressed at The Hahnemann Medical College & Hospital of Philadelphia, Philadelphia, Pa. 19102.

[1] *Abbreviations used in this paper:* MAC, membrane attack complex; PAS, periodic acid-Schiff; SLE, systemic lupus erythematosus.

Materials and Methods

Tissues. Renal tissue was obtained at autopsy (15 cases) and biopsy (7 cases) from patients with clinical and laboratory findings that fulfilled the American Rheumatism Association criteria for SLE (20). SLE renal disease was classified as mesangial nephropathy (2 cases), focal proliferative glomerulonephritis (7 cases), diffuse proliferative glomerulonephritis (10 cases), and membranous nephropathy (3 cases). The categorization of renal disease (21–23) was based on microscopic review of hematoxylin-eosin- and periodic acid-Schiff (PAS)-stained sections of autopsy tissues and renal biopsies performed before reference to the immunofluorescence data.

Clinical Data. 20 of 22 patients fulfilled previously described clinical criteria for active renal disease (24). One of two patients classified as mesangial nephropathy exhibited mild proteinuria (<1 g/24 h) and the second patient had no clinical evidence of renal dysfunction. One of the three patients with membranous nephropathy also had mild proteinuria and two patients had moderate to severe proteinuria (>3 g protein/24 h). Two patients manifested signs of acute renal failure, but microscopic examination of the kidneys obtained at autopsy did not show evidence of acute tubular necrosis, and no differences were observed between these and other patients with SLE nephritis with respect to interstitial and peritubular mononuclear infiltration. Four patients with diffuse proliferative glomerulonephritis were uremic before death and manifested signs of advanced diffuse proliferative glomerulonephritis on microscopic examination of their kidneys.

Antisera. Monospecific goat antisera to IgG, IgM, C3, and rabbit antisera to C1q (25) and C9 (26) were prepared and labeled with fluorescein (27). Antiserum titers were determined before labeling and expressed as the dilution of serum that produced a reaction of equivalence with 0.2 mg/ml of purified antigen: anti-IgG-1:5, anti-IgM-1:1, anti-C3-1:2, anti-C1q-1:1, and anti-C9-1:1, using agar gel double diffusion.

Antisera to C5b-9 neoantigen(s) were prepared in goats by injection of purified MAC (28) using a modification of published methods (29). Antisera showing precipitin reactivity with whole serum determined by agar gel diffusion were absorbed with human plasma coupled to cyanogen-bromide-activated Sepharose 4B-CL. Antisera that reacted with purified MAC, but not with serum precursor proteins were considered specific for neoantigen(s) of the MAC. Both agar gel diffusion and hemagglutination of sheep erythrocytes bearing the C5b-9 complex were used for assay (29). Fluorescein/protein ratios of the antisera were as follows: anti-IgG-2.2, anti-IgM-1.9, anti-C3-2.5, anti-C1q-2.2, anti-C9-2.5, and anti-neoantigen(s)-2.4. Each fluoresceinated antibody was used at a maximum dilution which gave a strong immunofluorescence reaction with positive control SLE kidney.

Microscopy. Renal tissue was quick-frozen in dry ice-isopentane at −90°C and sections were cut using a Harris cryostat (Harris Mfg. Co., Inc., N. Billerica, Mass.). Cryostat sections were studied by the direct immunofluorescence method and examined by epi-illumination using a Leitz orthoplan fluorescence microscope (E. Leitz, Inc., Rockleigh, N. J.). The tissue was photographed with Ektachrome 160 professional film (Eastman Kodak Co., Rochester, N. Y.). Specificity controls included the lack of reaction with three normal human kidneys and the inhibition of positive staining by prior absorption with purified antigen. Sections from formalin-fixed, paraffin-embedded tissue were stained with hematoxylin-eosin and PAS before examination by light microscopy. Electron microscopy was performed on sections of gluteraldehyde-fixed, plastic-embedded tissue from renal biopsies using a Zeiss EM9 electron microscope (Carl Zeiss, Inc., New York).

A comparison of the stability of immunoglobulins, complement components, and MAC in tissues was studied in three kidneys (cases 107, 117, and 118) that showed strongly positive immunofluorescence reactions for these proteins. Adherent cryostat sections were treated with 1 M NaCl, 0.2 M glycine, pH 2.4, 0.1% sodium dodecyl sulfate, or digested with 1 mg/ml of fungal proteinase K (Sigma Chemical Co., St. Louis, Mo.) for 3 h at 37°C and washed with phosphate-buffered saline. The sections were evaluated before and after these treatments for the presence of IgG, C3, and MAC.

Results

I. Immunopathology of the Glomerular Disease

A. MORPHOLOGIC FINDINGS. The classification of SLE nephritis was based on

glomerular alterations as previously described (21–23). Electron microscopic examination of glomeruli from five renal biopsies was consistent with the glomerular pathology observed by light microscopy.

B. IMMUNOFLUORESCENCE STUDIES. Glomerular localization of immunoglobulins, complement, and MAC is summarized in Table I. The intensity of immunofluorescence was graded as strong, moderate, and weak or absent in order to compare the relative amounts of detectable IgG, IgM, C1q, C3, and MAC, within each of the three groups of renal disease. No significant differences were observed between biopsy and autopsy specimens except for higher "background" staining for IgG and C3 in autopsy specimens. Sections from kidneys classified microscopically as focal proliferative glomerulonephritis revealed segmental immunofluorescence within mesangial areas and capillary walls (Fig. 1 A). The deposits were comprised of granular or

TABLE I

Glomerular Localization of Immunoglobulins, Complement, and MAC

Classification of glomerulonephritis		Relative intensity of fluorescence	Immunofluorescence demonstration of:				
			IgG	IgM	C1q	C3	MAC
Focal proliferative	(7)*	Strong	7‡	1	2	7	1
		Moderate	0	1	5	0	5
		Weak or absent	0	5	0	0	1
Diffuse proliferative	(10)	Strong	9	0	6	8	8
		Moderate	1	5	4	2	2
		Weak or absent	0	5	0	0	0
Membranous nephropathy	(3)	Strong	3	0	2	3	1
		Moderate	0	2	1	0	1
		Weak or absent	0	1	0	0	1

* Number of cases studied showing positive reaction.

‡ Number of cases showing reaction.

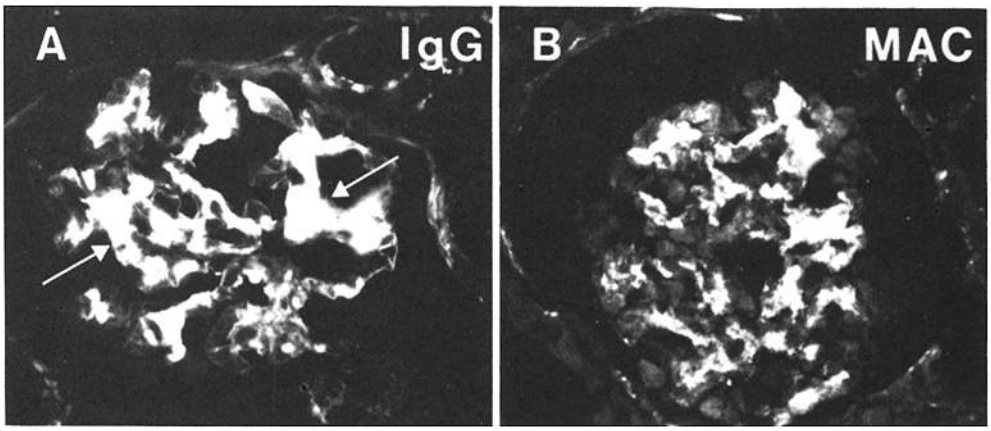

FIG. 1. Glomerular localization of IgG and MAC. Focal proliferative glomerulonephritis. (A) IgG. Extensive mesangial deposits (arrows) and segmental granular aggregates within capillary walls of glomerular tufts (× 400). (B) MAC. Similar distribution showing more discrete deposits with less intense fluorescence staining (× 400).

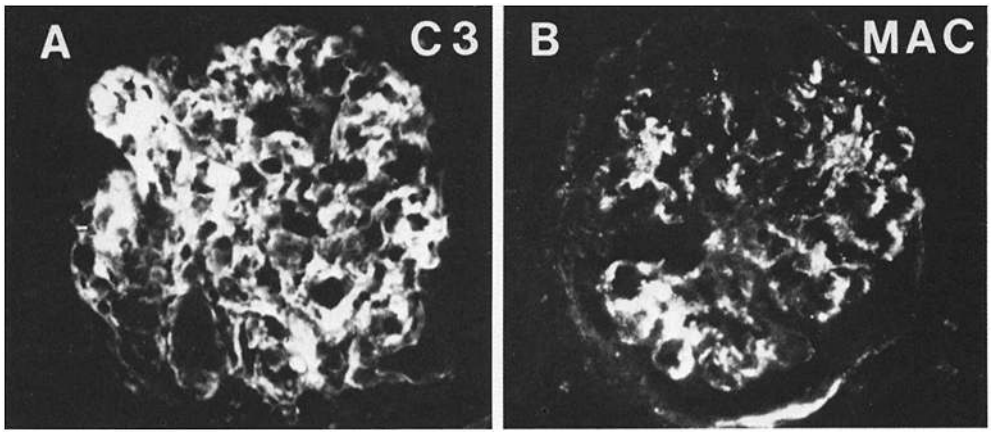

FIG. 2. Glomerular localization of C3 and MAC. Diffuse proliferative glomerulonephritis. (A) C3. Extensive granular and lumpy deposits similar to those found for IgG (× 400). (B) MAC. More extensive deposits than observed in Fig. 1 B, but less intense staining than evidenced in Fig. 2 A (× 400).

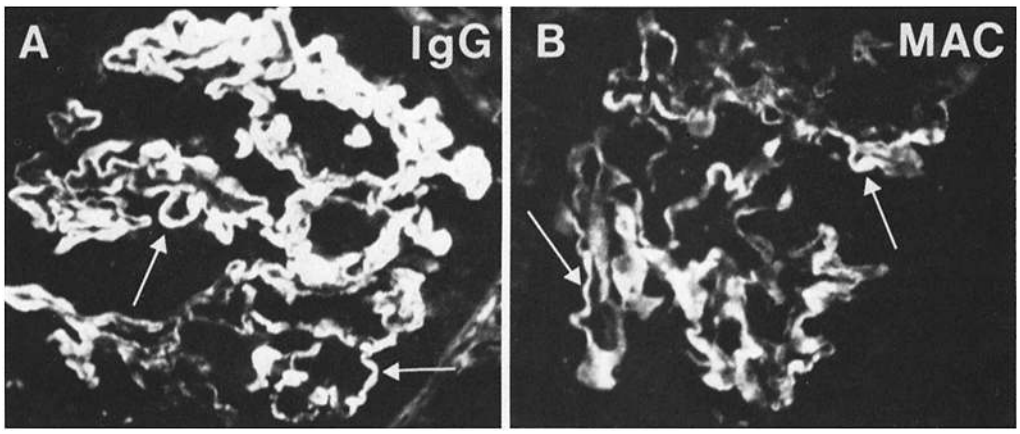

FIG. 3. Glomerular localization of IgG and MAC. Membranous nephropathy. Wire loop deposits along capillary walls of IgG (A), and MAC (B), showing similar distribution (× 400).

TABLE II

Peritubular Inflammation

	Number of cases studied	Tubules affected by infiltrate of mononuclear cells		
		+*	++	+++
Mesangial nephropathy	2	2	0	0
Focal proliferative glomerulonephritis	7	4	2	1
Diffuse proliferative glomerulonephritis	10	2	4	4
Membranous nephropathy	3	1	1	1

* +, <25%; ++, 25–50%; +++, >50%.

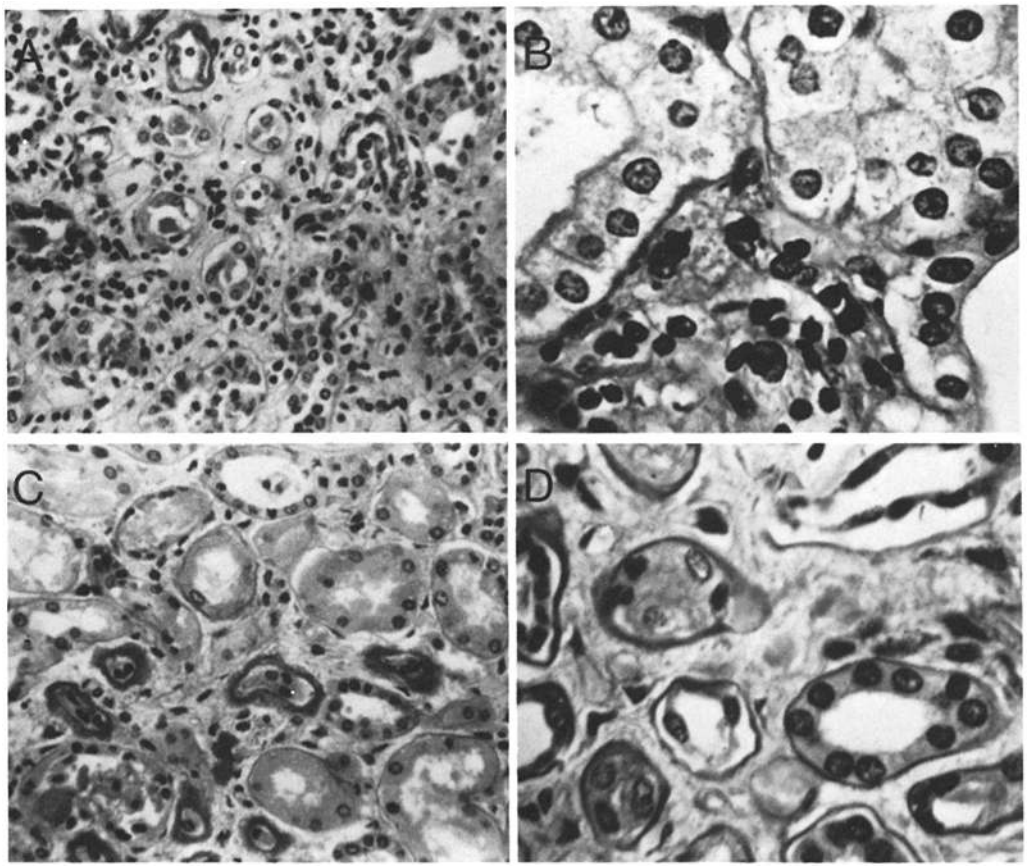

FIG. 4. (A) Diffuse infiltration of mononuclear cells surrounding proximal and distal convoluted tubules. Diffuse proliferative glomerulonephritis. PAS stain (× 150). (B) Mononuclear cell infiltrate contiguous to a proximal convoluted tubule. Focal proliferative glomerulonephritis. PAS stain (× 400). (C) Thickened peritubular basement membrane with atrophy of tubular epithelium, interstitial fibrosis and few inflammatory cells. Diffuse proliferative glomerulonephritis. PAS stain (× 250). (D) Higher power view of interstitial fibrosis and tubular atrophy. PAS stain (× 400).

irregular aggregates containing IgG, C3, and C1q, with lesser amounts of IgM, a pattern characteristic for immune complex localization. Kidneys with moderate to severe diffuse proliferative glomerulonephritis exhibited brighter immunofluorescence staining reactions, which were more diffuse and presented as larger confluent aggregates with a glomerular distribution similar to that of focal glomerulonephritis (Fig. 2A). Immunofluorescence demonstration of the MAC revealed more discrete deposits of lesser intensity for both types of glomerulonephritis (Figs. 1B and 2B).

Comparable immunofluorescence reactions were observed using either anti-C9 or anti-neoantigen sera for demonstration of MAC. The MAC, IgG, C1q, and C3 were detectable in a similar distribution indicating that immune complexes and the MAC were present in close proximity. This phenomenon was most clearly demonstrated in glomeruli from kidneys with membranous nephropathy. Diffuse subepithelial deposits with a granular or wire loop appearance contained both immune complexes and the MAC (Fig. 3). Higher resolution than can be achieved by fluorescence microscopy is

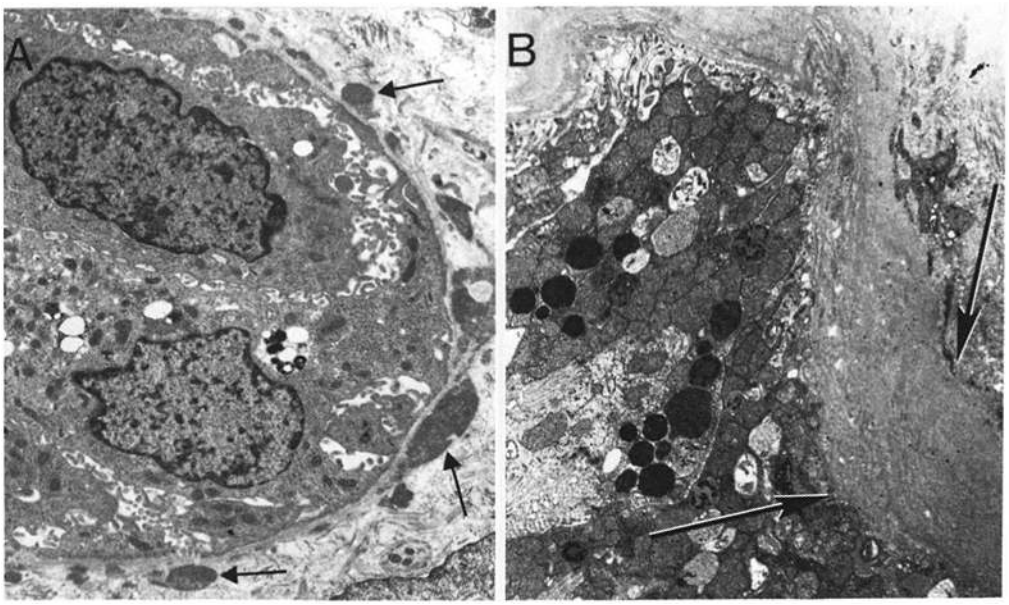

FIG. 5. Ultrastructure of peritubular region. Membranous glomerulonephritis. (A) Electron dense deposits located within and/or adjacent to tubular basement membrane. Appearance similar to subepithelial dense deposits found in glomeruli of the same biopsy (× 6,000). (B) The tubular basement membrane is thickened and frayed (arrow) (× 8,000). (Lead citrate, uranyl acetate.)

TABLE III

Peritubular Localization of MAC

Peritubular deposits of IgG and C3		Number of kidneys with peritubular MAC			Classification of renal disease			
		+*	++	+++	Mes‡	FP	DP	Mem
IgG, C3 absent	(7)§	3	3	1	2	2	2	1
IgG absent, C3+	(8)	2	3	3	0	2	5	1
IgG+, C3+	(5)	0	2	3	0	3	2	0
IgG+,++ C3++	(2)	0	1	1	0	0	1	1

* +, <25%; ++, 25–50%; +++, >50%.
‡ Mes, mesangial; FP, focal proliferative; DP, diffuse proliferative; Mem, membranous nephropathy.
§ Number of cases studied.

required for determination of the precise interrelationship between the MAC and antigen-antibody complexes.

II. Immunopathology of Renal Tubules

A. MORPHOLOGIC FINDINGS. Each of the 22 kidneys manifesting SLE nephritis showed several or more foci of peritubular inflammation (Table II). Diffuse proliferative glomerulonephritis was associated with the most severe inflammatory reactions. Focal and confluent areas of cellular infiltrate surrounded both proximal and distal convoluted tubules (Fig. 4A). In contrast, renal tissues showing focal proliferative glomerulonephritis or mesangial nephropathy contained discrete foci of inflammation predominantly in the region of proximal tubules (Fig. 4B). The infiltrates, whether

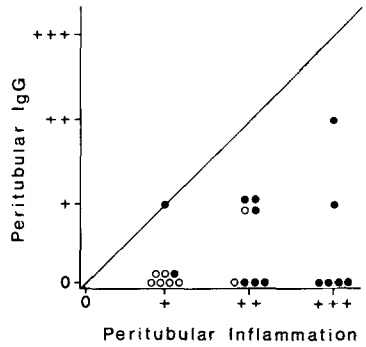

FIG. 6. Comparison of peritubular localization of IgG and cellular infiltrates for each case studied. Involved tubules graded as follows: +, <25%; ++, 25-50%; +++, >50% as determined by immunofluorescence or light microscopic examination. Autopsy (●). Biopsy (○).

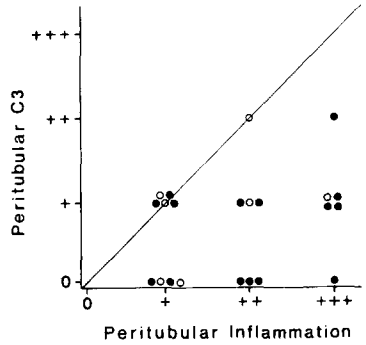

FIG. 7. Comparison of peritubular localization of C3 and cellular infiltration for each case studied. Involved tubules graded as follows: +, <25%; ++, 25-50%; +++, >50% as determined by immunofluorescence or light microscopic examination.

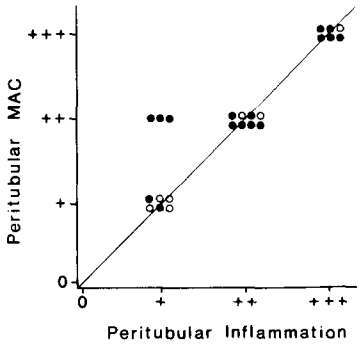

FIG. 8. Comparison of peritubular localization of MAC and cellular infiltration for each case studied. Involved tubules graded as follows: +, <25%; ++, 25-50%; +++, >50% as determined by immunofluorescence or light microscopic examination.

focal or diffuse, were composed primarily of lymphocytes, plasma cells, and scattered neutrophils. Both proximal and distal tubules within inflammatory areas showed degenerative changes marked by thickened basement membranes evident on PAS stain, as well as vacuolization and atrophy of the epithelium (Fig. 4C). Interstitial fibrosis (Fig. 4D) with obliteration of tubules was found only in kidneys with moderate

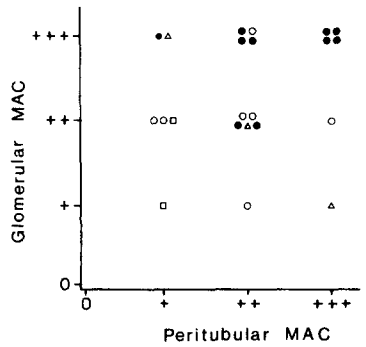

FIG. 9. Comparison of glomerular and peritubular localization of MAC for each case studied. Involved tubules graded as follows: +, <25%; ++, 25–50%; +++, >50% as determined by immunofluorescence and light microscopic examination. Peritubular MAC scored as in Fig. 1. Mesangial nephropathy (□); focal proliferative glomerulonephritis (○); diffuse proliferative glomerulonephritis (●); membranous nephropathy (△).

to severe proliferative glomerulonephritis. No microscopic evidence of acute pyelonephritis was observed, although the presence of chronic pyelonephritis or a primary interstitial nephritis could not be excluded. Tubules in five renal biopsies were examined by electron microscopy. Immune complex-type dense deposits analogous to those in glomeruli were demonstrated in only one biopsy (Fig. 5A), a case of membranous nephropathy. These deposits were found mainly peripheral to tubular basement membranes. Microscopically, a moderate number of inflammatory foci were present and IgG, C1q, C3, and the MAC were demonstrated in the peritubular region of this biopsy. Four biopsies manifested varying degrees of tubular basement membrane thickening with segmental fraying or splitting (Fig. 5B). Marked irregular thickening of the tubular basement membrane was found by electron microscopic examination in one patient with mild proteinuria, mesangial nephropathy, and isolated patches of the MAC without evidence of extra glomerular immunoglobulin or complement. Three other biopsies from patients with focal and diffuse proliferative glomerulonephritis and membranous nephropathy exhibited ultrastructural alterations in both proximal and distal tubular basement membranes associated with positive immunofluorescence for C3 and MAC. The limited number of tubules available for study in these biopsies precluded attempts to evaluate correlations between ultrastructural and immunofluorescence findings.

B. IMMUNOFLUORESCENCE STUDIES. Peritubular deposits of IgG and foci of C1q globulin were found in 7 of 22 cases (32%), whereas peritubular C3 and MAC were identified in higher incidence, 64% and 100%, respectively, in the 22 renal specimens studied (Table III). In contrast to IgG and C3, the MAC was closely correlated with foci of interstitial inflammation (Figs. 6–8). Control kidneys negative for peritubular MAC included three kidneys without renal pathology, two kidneys with benign arteriolonephrosclerosis, and two renal biopsies with focal glomerulonephritis (non-SLE). A poor correlation was found between glomerular and tubular MAC localization for individual patients, except for kidneys showing severe diffuse proliferative glomerulonephritis. These cases manifested extensive deposition of both peritubular and glomerular MAC (Fig. 9). A typical case of focal proliferative glomerulonephritis is shown in Fig. 10: absent peritubular IgG (Fig. 10A), small clusters of tubules

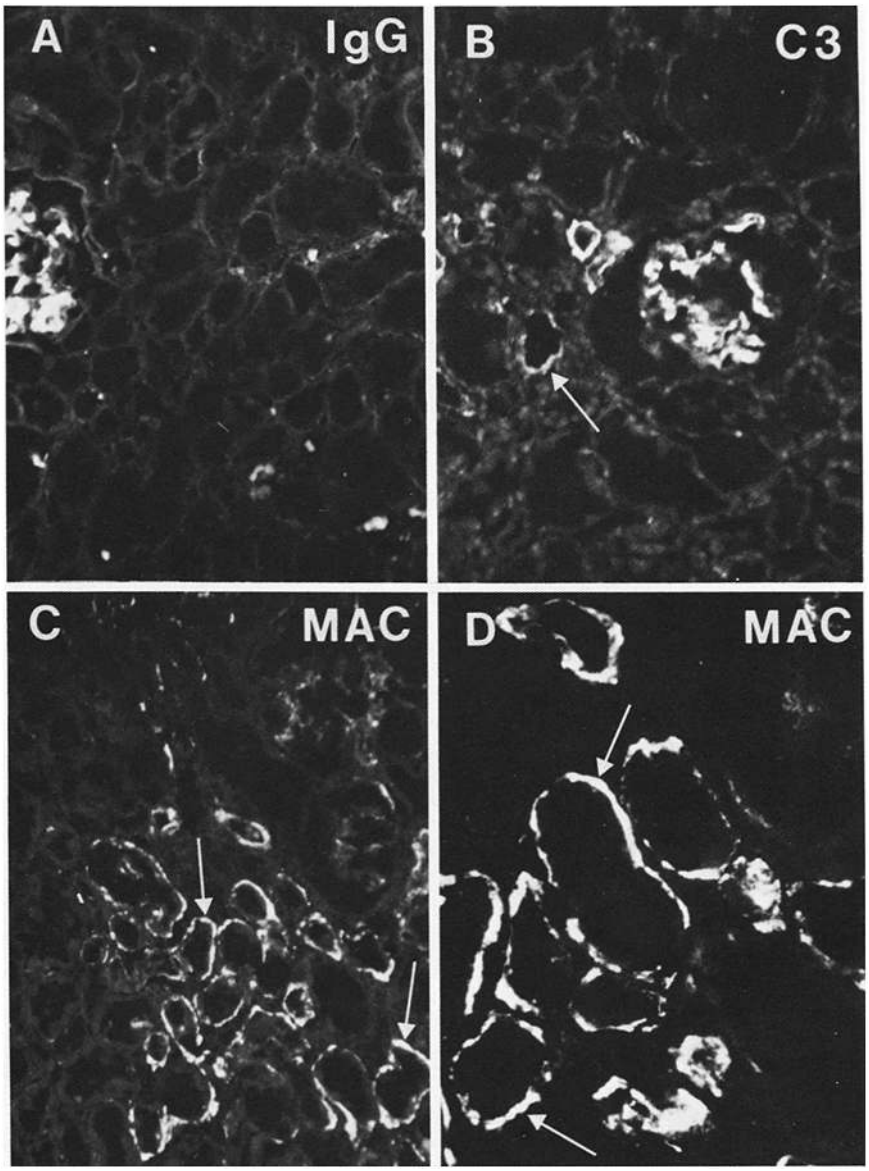

FIG. 10. Peritubular localization of immune complex and MAC. Focal proliferative glomerulonephritis. Photomicrographs A, B, C, and D taken from cryostat sections of the same tissue block. (A) Localization of IgG in glomeruli. Note absence of staining in peritubular region (× 150). (B) Localization of C3 in glomeruli and surrounding small group of tubules (arrow) (× 150). (C) Localization of MAC in glomeruli (upper right) with prominent peritubular deposits (center) (× 150). (D) Localization of peritubular MAC showing a discontinuous, thickened, linear pattern of deposits in the region of the tubular basement membrane (× 400).

surrounded by C3 (Fig. 10 B), and MAC deposits in the peritubular region of a larger group of renal tubules (Fig. 10 C). MAC localization varied from an irregular linear pattern with segmental areas of thickening (Fig. 10 D) to irregular, granular aggregates shown in Fig. 11.

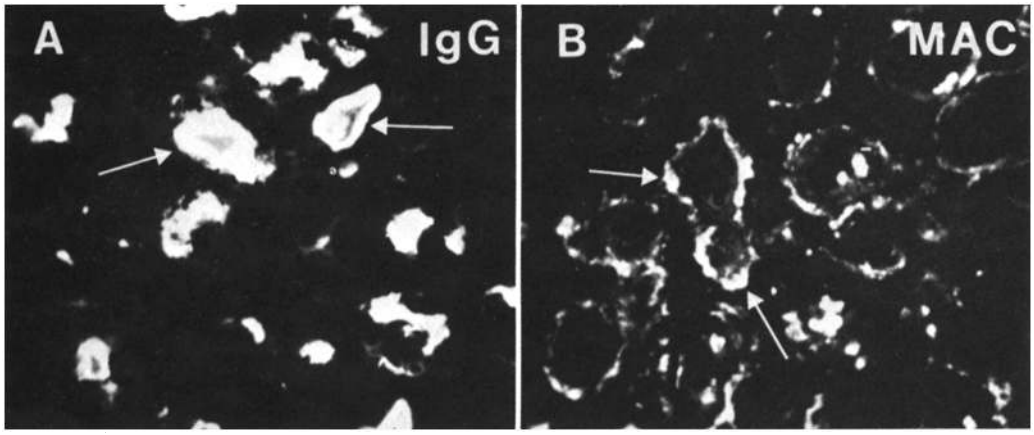

FIG. 11. Tubular localization of IgG and MAC. Diffuse proliferative glomerulonephritis. (A) IgG staining of intraluminal casts. Note absence of peritubular IgG (× 400). (B) Irregular granular aggregates of MAC surrounding tubules. Note the absence of staining of intraluminal casts (× 400).

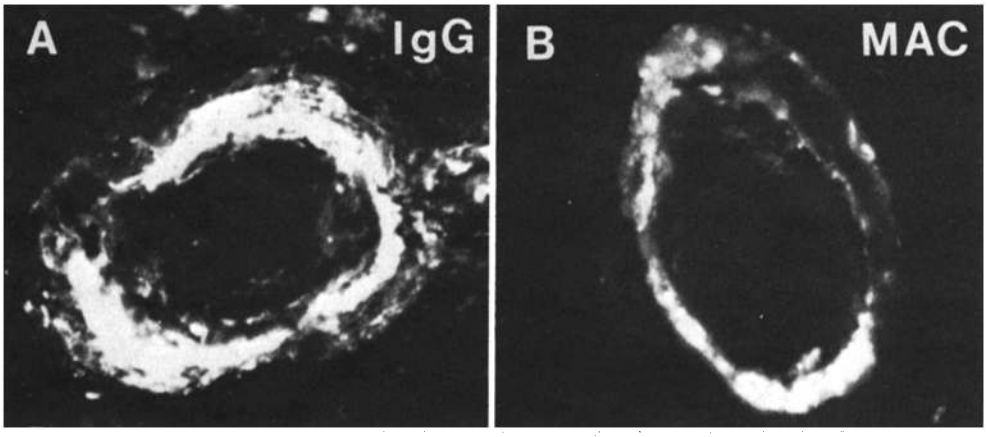

FIG. 12. Localization of IgG and MAC in the wall of a small artery. Diffuse proliferative glomerulonephritis. (A) Segmental deposition of IgG in an area of fibrinoid necrosis, and (B) of MAC showing a more granular appearance in the same area (× 400).

III. Immunopathology of Blood Vessels

Vascular deposits of immune complexes and MAC in vessel walls were most common in kidneys showing diffuse proliferative glomerulonephritis. Involvement of blood vessels ranged from small arterioles to medium sized arteries. IgG, C3, C1q, and the MAC were most prominent in vessel walls showing fibrinoid necrosis (Fig. 12). No attempt was made to quantitate the incidence of vessel involvement because of the focal nature of the vasculitis.

IV. Elution of Cryostat Sections

The intensity of immunofluorescence staining for IgG and C3 was markedly reduced after incubation of sections from three kidneys with acid glycine or sodium dodecyl sulfate. The intensity of fluorescence for the MAC was only slightly decreased. Digestion with protease for 1 h removed detectable IgG and C3, whereas the MAC

was not significantly affected.

Discussion

The MAC of complement was demonstrated by immunofluorescence at sites in renal glomeruli, blood vessels, and the periphery of proximal and distal convoluted tubules in kidneys with microscopic evidence of SLE nephritis. The renal lesions encompassed the spectrum of SLE kidney disease ranging from mesangial nephropathy to focal and diffuse proliferative and membranous glomerulonephritis. Glomerular deposits of immune complexes defined by the occurrence of IgG, C1q, and C3 were uniformly accompanied by MAC. This complex exhibited weaker immunofluorescence staining and more discrete deposits in glomerular capillaries and mesangial areas. Comparable amounts and a similar distribution were observed for immune complexes and MAC in the walls of blood vessels with fibrinoid necrosis. In contrast to the findings in glomeruli and blood vessels, a striking discordance was observed for the peritubular localization of MAC and immune complexes. Tubular deposits of MAC were present in kidneys of the 22 patients studied, whereas peritubular immune complexes were absent from 65% of the renal specimens examined. The MAC was observed in the tubular basement membrane region primarily in the form of segmental and irregular thickened linear deposits. Fragmentation and thickening of the basement membrane with subepithelial dense deposits were also observed by electron microscopic examination of renal biopsies in which the MAC deposits were demonstrated contiguous to tubules by immunofluorescence studies. Inflammatory changes within the interstitium were frequently associated with tubular MAC deposits, whereas a paucity of cellular infiltration was found in glomeruli even when heavy deposits of MAC were demonstrable.

The discordance noted for peritubular deposits of MAC and immune complexes may be explained by one or more of the following hypotheses: (*a*) Lesser amounts of peritubular immunoglobulin and complement are more amenable to metabolic degradation, whereas the MAC is intrinsically resistant to digestion by proteolytic enzymes (30). Insertion of MAC into the phospholipid membrane may also exert a protective effect (28). In vitro studies of cryostat sections incubated with acid and salt buffers, ionic detergents, or proteolytic enzymes indicated that MAC in tissue is a relatively stable complex. (*b*) Binding sites required for the demonstration of immune complexes may be masked or insufficient quantities of antigen-antibody complexes present for demonstration by immunofluorescence. (*c*) The alternative complement pathway may be more readily activated in tubulointerstitial regions by immunoglobulin-independent mechanisms, e.g., bacterial endotoxin (31), accounting for the failure to demonstrate peritubular IgG in most kidneys studied.

The association of MAC with tissue injury occurring in glomeruli and tubules suggests that this terminal complement complex may cause damage without intervention of proteases derived either from neutrophils or serum. The MAC appears to cause physical disruption of the plasma membrane by creating membrane defects (18). In tissue MAC may damage plasma membranes and interfere with normal cellular function by disturbing osmotic balance without overt membrane lysis. The affinity of MAC for phospholipid (32) may result in physical dissociation of the plasma membrane and alteration of cellular architecture. These changes have been observed at the muscle endplate in myasthenia gravis (33). In addition, the MAC binds to anionic

structures and may interact with nonphospholipid anionic sites located between epithelium and basement membranes (34).

Previous investigations have demonstrated that experimental immune complex glomerulonephritis in rabbits may progress despite depletion of neutrophils (35). The failure to observe significant neutrophil infiltration in most forms of human glomerulonephritis also suggests that other pathways contribute to tissue injury. Deposition of MAC and interaction with basement and, perhaps, cellular membranes may be a common pathway for mediation of tissue injury involving both immune and nonimmune initiated inflammatory lesions. Deposition of a complement component, C3, but not of immunoglobulin has been observed within myocardial infarction (36). Although the presence of MAC in necrotic myocardial tissue has not been assessed, activation of the alternative complement pathway by tissue breakdown products may result in assembly of the MAC.

The positive correlation between peritubular MAC and inflammation, independent of the presence of IgG and/or C3, suggests that this complex may be a more reliable marker for tissue injury. Tubulointerstitial nephritis studied by light, immunofluorescence, and electron microscopy (37, 38) has been stressed as a potentially important factor contributing to the destruction of renal parenchyma and the progression of glomerulonephritis (37). The demonstration of the peritubular MAC, an agent with known potential for damaging membranes, lends further support to this thesis. In one patient with proteinuria, immune complex deposits were limited to the glomerular mesangium, although peritubular MAC and ultrastructural thickening and fragmentation of tubular basement membrane were demonstrated. These findings raise the possibility that tubular dysfunction may have contributed to proteinuria. Tubular-associated immune complex deposits have been found in two patients with SLE and acute renal failure with histologically normal glomeruli. Heavy granular deposits of IgG, C1q, and C3 were observed surrounding damaged tubules, whereas glomerular deposits of IgG, C1q, and C3 were limited to mesangial areas (39). In the present study, the kidneys of two patients with acute renal failure showed concomitant glomerular disease and, therefore, the tubular contribution to renal failure was difficult to evaluate. The peritubular deposits in these patients showed no significant differences from those observed in patients without acute renal failure. Preliminary studies of kidneys exhibiting morphologic evidence of pyelonephritis indicate that MAC is predominantly interstitial and peritubular (G. Biesecker, S. Katz, and D. Koffler, unpublished observation), raising the possibility that tubular MAC in kidneys with SLE nephritis may reflect the occurrence of pyelonephritis as well as immune complex deposits. Although further studies are required to document the occurrence of subclinical interstitial pyelonephritis in patients with SLE, the consideration of this possibility has important therapeutic implications.

The emphasis on tubulointerstitial disease in human glomerulonephritis during the past 5–10 yr may represent a more precise evaluation of renal pathology or, alternatively, may reflect a subtle change in the nature of renal pathology in SLE. Formation of immune complexes with an increased predilection for tubular localization and/or an increased prevalence of subclinical pyelonephritis may have resulted from the utilization of more intensive immunosuppressive therapy. Experimental studies indicate that peritubular deposits are observed in most rabbits effected by chronic serum sickness disease induced by bovine serum albumin immunization (40) and may also

be found in animals immunized with homologous kidney (41, 42). Therefore, immune complexes containing either exogenous or homologous antigens are capable of inducing extraglomerular lesions analogous to those found in the tubulointerstitial region of kidneys manifesting SLE nephritis. However, the uniform presence of IgG in the experimental renal lesions but not in the tubulointerstitial lesions of SLE suggests that several mechanisms are operative in the induction of tubular lesions found in SLE patients. Studies are currently being performed in an attempt to identify alternative complement pathway components as well as bacterial antigens in the renal interstitium of kidneys with SLE nephritis.

Parallel studies of the skin of patients with SLE indicate that the presence of MAC is associated with tissue injury. Clinically and microscopically uninvolved skin manifests IgG and C3 containing immune complex deposits at the dermal-epidermal junction in >50% of patients with SLE particularly in association with renal disease (43, 44). A comparison of early acute inflammatory skin lesions with "normal" skin in patients with SLE indicates that MAC is present in the former and absent from the latter.[2] Therefore, the terminal complement complex is present at sites containing antigen-antibody complexes only when there is concomitant inflammation. These preliminary data provide additional support for the thesis that MAC is both a marker for demonstration of tissue injury and a mediator of the inflammatory response in SLE nephritis.

Summary

The membrane attack complex (MAC) of the complement system was localized in both glomeruli and peritubular regions of 22 kidneys manifesting systemic lupus erythematosus (SLE) nephritis. A similar distribution was observed for immune complex markers (IgG, C1q, and C3) and MAC in glomeruli, although the deposits of MAC were more discrete and showed lesser immunofluorescence staining intensity compared with immunoglobulins and complement components. In contrast, peritubular immune complexes were present in only 7 out of 22 kidneys, involved comparatively small clusters of tubules, exhibited weaker immunofluorescence staining than MAC, and failed to correlate with interstitial foci of inflammation. Granular or irregular linear aggregates of the MAC were observed at the periphery of larger groups of tubules contiguous to areas of interstitial inflammation. Comparable amounts of IgG, C1q, C3, and MAC were present in blood vessel walls in areas of fibrinoid necrosis. These data suggest that the MAC is a direct mediator of tissue injury occurring in renal glomeruli, tubules, and blood vessels. The discordance between immune complexes and MAC localized in the peritubular region, but not in glomeruli or blood vessels, raises the possibility that both immune complexes and nonimmune agents, such as bacterial antigens, may activate the classical or alternative complement pathways and thereby play a role in the pathogenesis of tubulointerstitial lesions of SLE nephritis.

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