Acute Glomerulonephritis

Nobuyuki YOSHIZAWA

Abstract

Acute glomerulonephritis (AGN) is a representative disease of acute nephritic syndrome characterized by the sudden appearance of edema, hematuria, proteinuria, and hypertension. The prototype of AGN is acute poststreptococcal glomerulonephritis (APSGN). "Nephritogenic streptococci" are defined as organisms that are cultured from a patient who develops AGN. Although only a limited number of M-types of streptococci have been recognized as "nephritogenic streptococci", all M-types of streptococci may have nephritogenic potential because the genes for major putative nephritogenic antigens such as SPEB and NAPlr are found to be present in all group A streptococci thus far examined. Pathogenic mechanisms for APSGN involving both humoral and cell-mediated immunity have been recently proposed. The role of humoral immunity is presumed to be mediated by the *in situ* formation of nephritogenic streptococcal antigen-antibody complexes and circulating immune complexes. While in the cellular immune component a role for delayed-type hypersensitivity has been suggested to contribute to the pathogenesis of APSGN.
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Key words: APSGN, humoral immunity, delayed type hypersensitivity, nephritogenic antigen

Introduction

Acute glomerulonephritis is a representative disease of acute nephritic syndrome characterized by the sudden appearance of edema, hematuria, proteinuria, and hypertension. The differential diagnosis of this syndrome is listed in Table 1 (1).

Over 200 years ago von Plenciz et al (2) reported edema, oliguria, and colored urine appearing after a latent period among patients with scarlet fever. This was the first observation linking renal disease with streptococcal infection. In the 19th century, Bright (3) published the first studies on morphologic changes in glomerulonephritis. In 1923 Dicks (4) and Dochez and Sherman (5) established that β-*hemolytic streptococcus* was the etiologic agent of scarlet fever. In 1929 Longcope (6) described the association between acute glomerulonephritis and upper respiratory tract infections from which β-*hemolytic streptococci* were cultured, and in 1938 Lyttle et al (7) documented streptococcal infections in 94 percent of 116 consecutive cases of acute glomerulonephritis. In 1940 Futcher (8) described 153 cases of glomerulonephritis and found that 7.2 percent followed skin infections; furthermore, he noted that the skin was the site of infection in 4.7 to 28 percent of the cases in the series reported in the preceding 28 years.

The major focus of this review is on epidemiology, pathogenesis and nephritogenic antigens of acute poststreptococcal glomerulonephritis (APSGN); this is the prototype, and it is distinguished from the other types of acute glomerulonephritis by its typical serologic, histologic, and chronologic features.

Epidemiology

There has been a gradual decrease in the incidence of poststreptococcal sequelae in Japan, the United States, Central Europe, and Great Britain during the last two to three decades. Nevertheless, APSGN continues to have a wide distribution, as indicated by reports of the disease from all over the world (9).

The disease is more frequent among children between the ages of 2 and 12 years but, in most large series, 5 to 10 percent of the patients are older than 40 years and 5 percent are younger than 2 years of age (9). There is a male preponderance in cases with symptomatic acute nephritis, but when subclinical disease as well as clinical disease are taken into account, the difference disappears (9).

Since streptococcal infections could be associated with rheumatic fever or glomerulonephritis, but not with both, and the epidemic characteristics of these nonsuppurative complications were different, Seegal and Earle (10), Rammelkamp, Weaver, and Dingle (11) postulated that only certain streptococcal strains were capable of causing nephritis. Subsequent clinical and epidemiologic observations (12–14) confirmed this concept, and a considerable amount of effort has been devoted to elucidate what makes streptococci nephritogenic. At present, this remains a matter of controversy. By definition, nephritogenic streptococci are organisms that are cultured from a patient who develops acute glomerulonephritis. Clearly, the presumption of a causative role is on firmer grounds if the observations are made

From the Department of Public Health, National Defense Medical College, Saitama
Reprint requests should be addressed to Dr. Nobuyuki Yoshizawa, the Department of Public Health, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513

Table 1. Differential Diagnosis of Acute Glomerulonephritis (24)

Low serum complement level	Normal serum complement level
SYSTEMIC DISEASES	
Systemic lupus erythematosus (focal, 75%; diffuse, 90%)*	Polyarteritis nodosa group
Subacute bacterial endocarditis (90%)	Hypersensitivity vasculitis
Visceral abscess	Wegener's granulomatosis
"Shunt" nephritis (90%)	Henoch-Schönlein purpura
Cryoglobulinemia (85%)	Goodpasture's syndrome
RENAL DISEASES	
Acute postinfectious glomerulonephritis (>90%)	IgA (or IgG-IgA) nephropathy
Membranoproliferative glomerulonephritis	Idiopathic rapidly progressive glomerulonephritis (RPGN)
Type I (50%–80%)	Anti-GBM disease
Type II (80%–90%)	Negative immunofluorescence findings
	Immune complex disease

GBM: glomerular basement membrane. *Percentages indicate the approximate frequencies of C3 or hemolytic complement levels.

in epidemic conditions than if the association is detected only in sporadic cases. The M and T proteins located in the bacterial wall have been used for characterizing the microorganism and its infectivity. It is recognized that M-types 1, 2, 4, 12, 18, 25, 49, 55, 57, and 60 may have nephritogenic potential (15) and specific M-types, such as 49, 55, 57, and 60 usually are associated with postpyoderma nephritis (16). In addition, nontypeable group A streptococci are frequently isolated from the skin or throat of patients with glomerulonephritis, representing presumably unclassified nephritogenic strains. The overall risk of developing nephritis after infection with nephritogenic streptococci is about 15 percent (16), but the risk of nephritis may be related to the M-type and the site of infection. For example, type 49 streptococcal infection carries a 5 percent risk of nephritis if present in the throat and 25 percent if the infection occurs in skin (17).

Poststreptococcal nephritis usually occurs as sporadic cases, but epidemic outbreaks have taken place in "closed" communities (18, 19) or in rural and city areas that have poor hygienic conditions, or within clusters of densely populated dwellings (20, 21). High incidence of malnutrition, anemia, and intestinal parasites are common characteristics of communities in which APSGN is endemoepidemic. In certain areas, such as Trinidad (20) and Maracaibo (21), epidemics may occur in cyclic outbreaks every 5 to 7 years, a circumstance that has not been completely explained. The epidemic and endemic incidence in areas within a city appear to be closely correlated (21).

It has been recognized that sporadic APSGN following upper respiratory infection, pharyngitis, and tonsillitis is more frequent in the winter and spring in temperate areas, whereas skin infection more commonly precedes APSGN in the more tropical and subtropical areas, with a peak incidence during summer and fall (13, 16).

Pathogenesis

The importance of both humoral and cellular immunity in the pathogenesis of APSGN have been recently proposed. The role of humoral immunity in APSGN is presumed to be mediated by the *in situ* formation of nephritogenic streptococcal antigen-antibody complexes (22) and circulating immune complexes (23). A popular and theory (24) is that nephritogenic streptococci produce proteins with unique antigenic determinants which have a particular affinity for sites within the normal glomerulus. Following release into the circulation, they encounter and lodge within the glomerulus, binding to sites for which they have an intrinsic affinity. Once bound to the glomerulus, they activate complement directly by interaction with properdin (25) (Fig. 1), thus leading to triggering of the alternate pathway. These glomerular-bound streptococcal proteins also serve as fixed antigens for subsequent immune complex formation with circulating anti-streptococcal antibodies. The latter event leads to additional complement fixation via the classical pathway which, in turn, leads to the generation of additional inflammatory mediators and recruitment of inflammatory cells.

Other possible mechanisms for APSGN would involve streptococcal infection as an etiologic mechanism but would not implicate immune complex-containing streptococcal antigens in development of glomerular immune deposits. McIntosh et al (26), and Kanwar et al (27) have postulated that the antigen in APSGN is autologous IgG altered by exposure to streptococcal neuraminidase. The modified IgG becomes antigenic and elicits an anti-IgG rheumatoid factor response, which may lead to the formation of cryoglobulins. This is in accord with the observation that IgG eluted from glomeruli in APSGN has rheumatoid factor activity but no detectable antibody to known streptococcal antigens (28, 29). However, neuraminidase is produced by non-nephritogenic streptococci as well, and patients

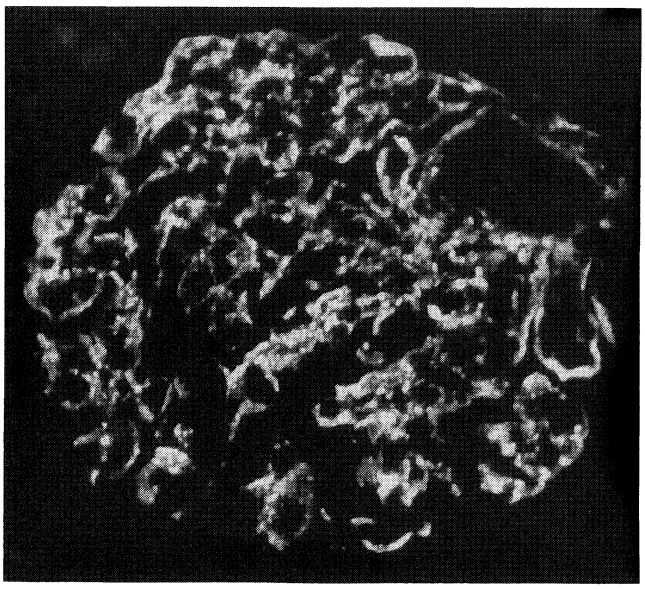

Figure 1. Glomerular deposition of properdin in APSGN (×250).

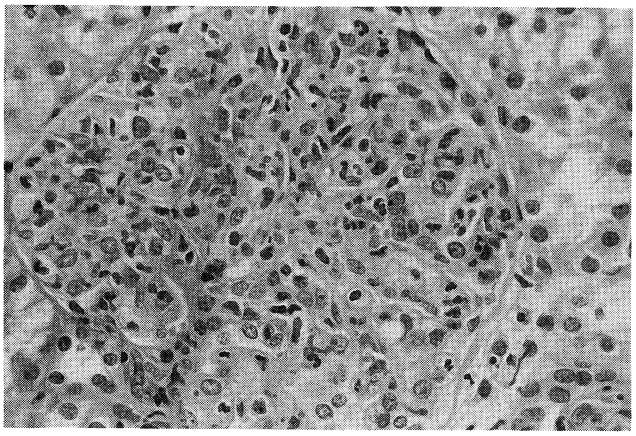

Figure 2. Polymorphonuclear leukocyte and monocyte infiltration in APSGN (From Reference 33, Yoshizawa et al. Cell-mediated immune response in acute poststreptococcal glomerulonephritis. Jpn J Nephrol 36: 322–330, 1994) (×200).

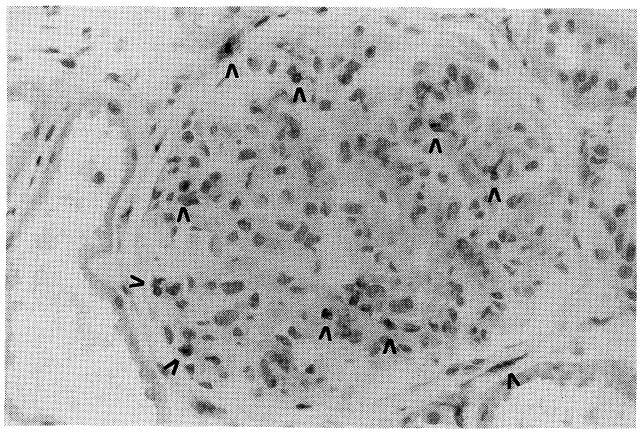

Figure 3. Helper/inducer T cells in APSGN (From Reference 33) (×200).

with streptococcal infection without nephritis may also have cryoglobulins and rheumatoid factor (30). Moreover, experimental glomerulonephritis induced with cationized IgG results in a primarily membranous type of lesion (31, 32).

A role for delayed-type hypersensitivity (DTH) has also been implicated in the glomerular manifestations of this disease (33, 34). In the early stage of disease, resident endothelial and mesangial cells are prominently proliferated and this is accompanied by infiltration with polymorphonuclear leukocytes and monocytes (Fig. 2). Macrophages (Mϕ) are important effector cells which cause resident cell proliferation in APSGN. Mϕ infilitration in the glomeruli appears to be mediated by complement-induced chemotaxis and probably an antigen-specific event related to the DTH mediated by helper/inducer T cells (Figs. 3, 4). Recently, Mϕ have been reported to be a source of host plasminogen activators at sites of infection (35).

Another recent observation of potential relevance to the pathogenesis of APSGN is that both streptococcal M proteins and pyrogenic exotoxins can act as superantigens. These products can cause a marked expansion of T cells expressing specific T-cell receptor β-chain variable gene segments (36–38). Superantigens can induce a selective increase in T-cell receptor β+cells and massive T-cell activation, with release of T cell-derived lymphokines such as interleukin 1 and interleukin 6 (39–41). Superantigens also induce polyclonal B-cell activation and production of auto-antibodies (42). Elevated levels of the inflammatory cytokines (interleukin 6 and tumor necrosis factor-α) have been reported in APSGN (43). A role for *methicillin-resistant Staphylococcus aureus* (MRSA) in the pathogenesis of a postinfectious immune complex nephritis via a superantigen mechanism has been suggested (44). Cryoglobulins, rheumatoid factors, and other autoimmune phenomenon do occur in APSGN, and a role for streptococcal superantigens in the initiation of glomerulonephritis is worthy of further study.

Nephritogenic Antigens

There are presently two known major putative nephritogenic antigens that have been identified, SPEB (also described as NSAP or NPBP) and NAPlr. Villarreal et al (45), in Zabriskie's laboratory, previously identified an extracellular protein unique to nephritogenic strains from cultures of type 12 organisms. This protein, called nephritis strain-associated protein (NSAP), was noted in 56% of renal biopsies with signs of poststreptococcal glomerulonephritis. NSAP was not detected in biopsies from patients with other forms of nonstreptococcal glomerulonephritis or rheumatic fever. The vast majority of patients with glomerulonephritis has serum antibodies to NSAP

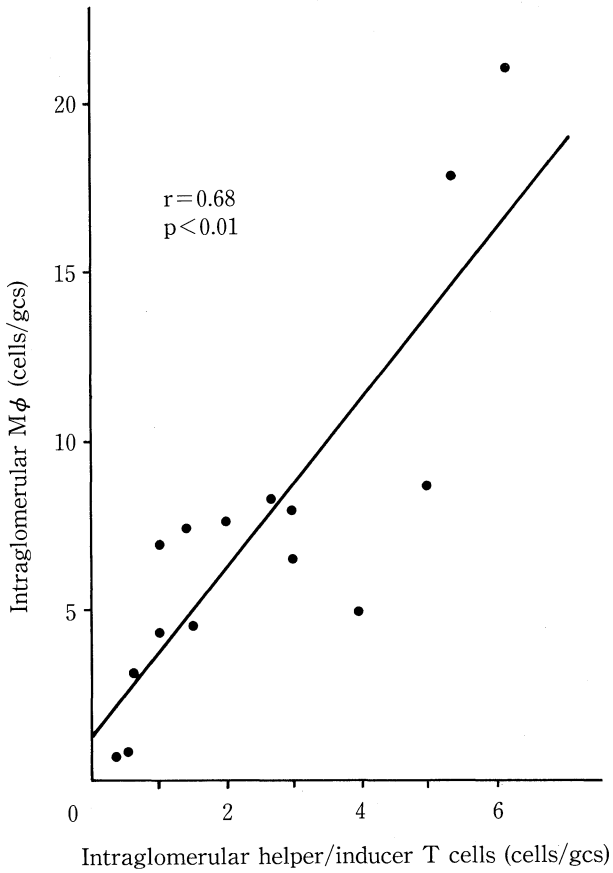

Figure 4. Correlation between intraglomerular Mϕ and helper/inducer T cells in APSGN (From Reference 33).

(46). The molecule has been isolated and purified, and it has a subunit of 46 kDa. (47). NSAP has antigenic, biochemical, and structural similarities to streptokinase from group C streptococcal organisms, and it binds to plasmin and is a plasminogen activator. This protein is not related to group A streptokinase (48) or to a recently described streptococcal dehydrogenase protein according to these authors (48, 49). Investigation into the amino acid sequence and immunologic reactivities suggests that this protein is the streptococcal pyrogenic exotoxin B precursor (previously termed zymogen-streptococcal proteinase precursor). Vogt et al (50, 51) isolated and identified a number of different cationic proteins from nephritogenic streptococci. Cationic moieties are known to have affinity for the GBM. Antibodies raised against these cationic proteins enabled Vogt et al to demonstrate the presence of these protein antigens (or a cross-reactive antigen) in almost half the renal biopsies from patient with APSGN. Serum antibodies to these cationic antigens were noted in the patients with poststreptococcal glomerulonephritis. The cationic antigens were not identified in renal biopsy specimens that show signs of immune complex (but nonstreptococcal) glomerulonephritis. The authors suggested that this antigen possibly initiated acute glomerulonephritis by means of in situ immune complex formation.

Table 2. Immunofluorescent Results of Staining for SPEB in APSGN and Non-APSGN Biopsies (52)

Biopsy specimens	Anti-SPEB (+)	Anti-SPEB (–)	Total
APSGN	12 (67%)	6 (33%)	18
Non-APSGN[a]	4 (16%)	21 (84%)	25

p=0.0007 (chi-square analysis). Abbreviations are: SPEB: streptococcal proteinase, ASPGN: acute post-streptococcal glomerulonephritis. [a]Defined as normal kidney tissue, membranous nephropathy, IgA nephropathy, vasculitis, minimal change, lupus nephritis, nephrosclerosis, ischemic renal disease, crescentic GN, interstitial nephritis, or thin basement membrane disease

Poon-King et al reported a nephritis plasmin binding protein (NPBP) (49). This protein is a 46 kDa protein secreted by nephritogenic strains and has properties identical to NSAP described by Villarreal et al (45). This protein binds to human plasmin and reacts preferentially with antibodies in APSGN sera. Amino acid sequence analysis indicated that NPBP was a streptococcal pyrogenic exotoxin B (SPEB) precursor. Cu et al (52) showed that anti-SPEB antibody were present in the serum of patients with APSGN and antibody titers were significantly higher than in acute rheumatic fever, scarlet fever or normal sera. When kidney biopsies were probed with rabbit anti-SPEB antibody, 12 of 18 (67%) of the APSGN cases were positive, while only 4 of 25 (16%) of the non-APSGN cases were positive (Table 2). Parra et al (53) suggested that increased anti-zymogen (SPEB precursor) antibody titers were the best available marker for streptococcal infection associated with acute glomerulonephritis (Fig. 5). Taken together, these findings suggest that this toxin plays a significant role in the pathogenesis of APSGN.

Traditionally, streptococcal M-protein has been thought to be the relevant antigenic bacterial fraction (54). M-protein fractions can complex with fibrinogen and localize in glomeruli (55, 56), and glomerulonephritis can be induced with injection of M-protein-M-protein/fibrinogen complexes (57). M-protein may be antigenically cross-reactive with the GBM (58). However, Treser et al (59) have suggested that the nephritogenic fraction is different from the M-protein. Glomerular sections of patients with early APSGN can be stained by FITC-labeled IgG obtained from the serum of patients convalescing from APSGN (60). Localization of the antigenic sites was found on the endothelial side of the glomerular basement membrane and in the mesangial matrix by immunofluorescein and immunoferritin technics (61). The fact that this serum had these antibodies independent of the M type of the original infection suggested that a non-M antigen was present in the glomerulus.

Endostreptosin was obtained after disruption of nephritogenic streptococci, and it had the ability to preabsorb the specific antibody of convalescent sera (62). This antigen is demonstrable in the glomerulus only during the initial phase of acute glomerulonephritis and reacts with antibodies present

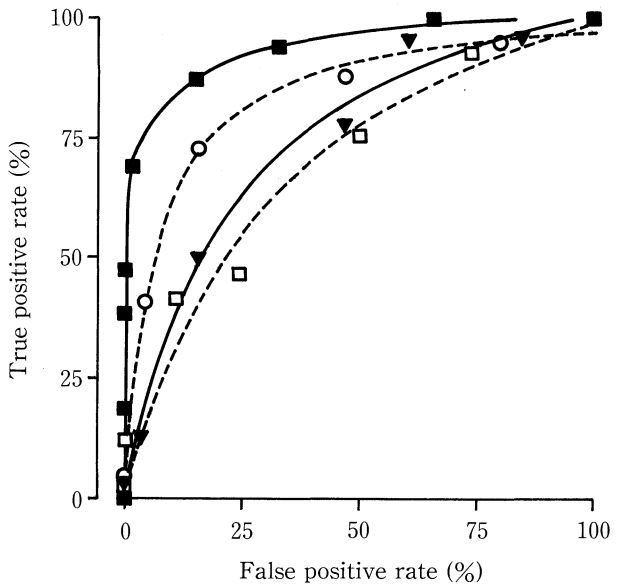

Figure 5. Receiver operating characteristics (ROC) curve for the four antibody tests on samples from Venezuela. Anti-zymogen and antiproteinase curves are drawn with uninterrupted lines. Anti-zymogen titers are superior to the rest at all levels of the curve. Symbols are: (■) anti-zymogen; (○) anti-DNAseB; (▼) anti-proteinase; (□) anti-streptolysin. (This figure was reproduced with permission from Parra et al. and Blackwell Science, Inc. Antibody to streptococcal zymogen in the serum of patients with acute glomerulonephritis: A multi-centric study. Kidney Int 54: 509–517, 1998. Reference 53.)

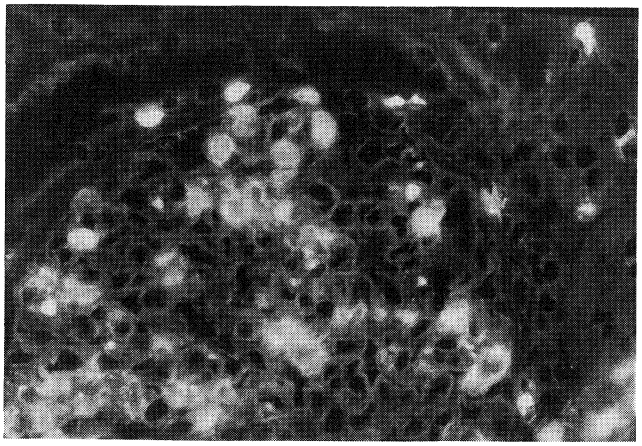

Figure 6. Glomerular deposition of NAPlr in APSGN. (From Reference 68, Yamakami et al. The potential role of nephritis-associated plasmin receptor (NAPlr) in acute poststreptococcal glomerulonephritis. in: Methods, 2000) (×400).

in the convalescent sera of patients with acute glomerulonephritis. In the late phases of the disease, the antigen can no longer be detected, presumably because all the previously noted antigenic sites have been covered by the specific antibody. Endostreptosin's molecular weight is between 40 and 50 kDa and is most likely derived from the streptococcal cytoplasm. Seligson et al (63) have suggested that acute elevations of endostreptosin titers are generally diagnostic of APSGN. Although low titers of antibody have been found in as many as 70% of normal individuals, significantly higher titers of antibodies are found in patients with poststreptococcal glomerulonephritis. The majority of patients with acute rheumatic fever do not have these high levels of antibody titer. Thus, Lange et al (64) believe that elevated levels of antibody to endostreptosin are diagnostic of postinfectious glomerulonephritis and are correlated well with the course of the pathologic disease process.

This factor is similar to the preabsorbing antigen (PA-Ag) described by Yoshizawa et al (65). A unique streptococcal antigen (PA-Ag) was found by immunofluorescence using labeled rabbit antiserum against PA-Ag in the glomeruli of kidney biopsy specimens from patients early in the APSGN disease course (65). Ouchterlony immunodiffusion analysis demonstrated antibody to PA-Ag only in the serum of patients with APSGN, while serum of patients with streptococcal infections without renal complications did not contain this antibody. The PA-Ag was purified by column chromatography followed by isoelectric focusing and was found to have a molecular weight 43 kDa and a pI of 4·7. The purified protein selectively absorbed the staining capacity of FITC-labeled IgG from the serum of convalescent patients and thus prevented glomerular staining. PA-Ag was shown to activate an alternative pathway of complement, as measured by the conversion of factor C3 to C3i and B to Bb *in vitro*. The demonstration that PA-Ag was present in the glomeruli during the early phase of APSGN, coupled with its ability to activate complement, suggested that it must be involved in the pathogenesis of APSGN. In 1997, an experimental model of APSGN was established using crude PA-Ag, which confirmed the nephritogenicity of this antigen (66).

Recently Yoshizawa et al (67, 68) isolated NAPlr and noted this antigen was present in 100% of the early APSGN glomeruli (Fig. 6). The antigen was purified by affinity chromatography using APSGN IgG immobilized Sepharose followed by anion-exchange chromatography. Purification was monitored by ELISA and Western blotting using the binding characteristics of the specific antibodies present in APSGN serum. The molecular weight of the purified antigen, termed nephritis-associated plasmin receptor (NAPlr), was 43 kDa and the internal amino acid sequence was found to be homologous to plasmin receptor (Plr) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) of group A streptococci strain 64/14 (69, 70) (Fig. 7). The purified NAPlr exhibited GAPDH activity and plasmin(ogen) binding activity. Using FITC-labeled polyclonal anti-NAPlr, the antigen was found to be present in the glomeruli of 22/22 patients in the early stage of APSGN (Table 3). Streptococcal Plr was also demonstrated in human APSGN glomeruli for the first time using monoclonal anti-

VVKVGINGFGRIGRLAFRRIQNIEGVEVTRINDLTDPNMLAHLLKYDTTQGRFDGTV
EVKEGGFEVNGNFIKVSAERDPENIDWATDGVEIVLEATGFFAKKEAAEKHLHANGA
KKVVITAPGGNDVKTVVFNTNHDILDGTETVISGASCTTNCLAPMAKALHDAFGIQK
GLMTTIHAYTGDQMILDGPHRGGDLRRARAGAANIVPNSTGAAKAIGLVIPELNGKL
DGAAQRVPVPTGSVTELVVTLDKNVSVDEINSAMKAASNDSFGYTEDPIVSSDIVGV
SYGSLFDATQTKVMEVDGSQLVKVVSWYDNEMSYTAQLVRTLEYFAKIAK

Figure 7. Amino acid sequence of plasmin receptor from group A streptococci strain 64/14. (From Reference 69, Lottenberg et al. Cloning, sequence analysis, and expression in *Escherichia coli* of a streptococcal plasmin receptor. J Bacteriol 74: 5204–5210, 1992.)

Table 3. Detection of Glomerular NAPlr (68)

	NAPlr
APSGN (1–32 days)	31/40 (78%)
1–14 days	22/22 (100%)
15–32 days	9/18 (50%)
Non-APSGN	4/100※ (4%)
Normal kidneys	0/10

※ Positive cases are found in MPGN (2/10), HSPN (1/10), Lupus N (1/10), FSGS (0/10), RPGN (0/10), IgAN (0/10), Non-IgAN (0/10), MN (0/10), MCNS (0/10) and DN (0/10).

body to the recombinant Plr protein. Antibody to NAPlr was found in the sera of 46 out of 50 (92%) patients within 3 months of onset.

A mechanism for APSGN is proposed in Figure 8 (68). Soluble, released NAPlr would be expected to bind to glomeruli and provide a mechanism to capture plasmin activated by streptokinase. The activated plasmin bound to NAPlr associates with GBM and mesangium. Bound plasmin is not regulated by host physiological inhibitors like α_2 antiplasmin, and can thus cause tissue destruction by direct action on basement membranes or by indirect activation of procollagenases and other matrix metalo-proteinases (71–73). NAPlr can also participate in alternate complement activation, which leads to accumulation of polymorphonuclear cells and macrophages and to local inflammation. Finally, the *in situ*-formed and circulating immune complexes can readily pass through the altered GBM and accumulate on the subepithelial space as humps.

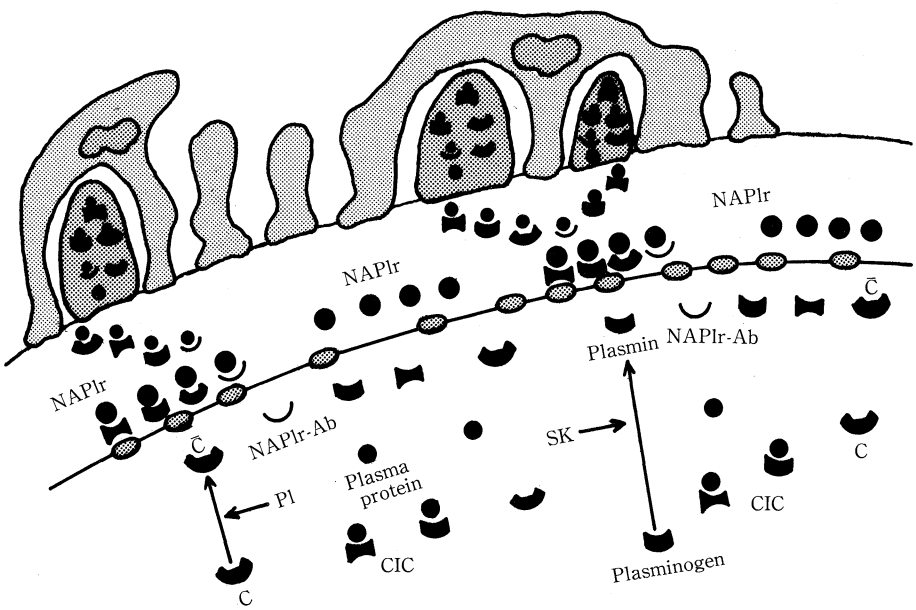

Figure 8. The schematic representation of proposed mechanism for APSGN. C: complement, C̄: activated complement, Pl: plasmin, NAPlr: nephritis-associated plasmin receptor, SK: streptokinase, CIC: circulating immune complex (From Reference 68).

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