Table 1. (Continued)

45	15	f	130/70	0	270	162	MCD	2	2	3	2	1	0	Pr	9	Normal
46	12	m	120/66	0	270	140	FSGS	0	1	3	2	1	0	Pr	10	HD
47	13	m	116/62	0	1500	128	MCD	0	0	2	0	1	0	Pr	3	Normal
48	5	m	90/40	0	2000	100	MCD	0	0	2	0	2	0	Pr + CyA	3	Normal
49	10	f	90/52	0	300	131	MCD	0	0	3	2	1	0	Pr	7	Frequent
50	4	m	98/46	0	300	115	MCD	2	0	3	2	2	0	Pr + CyA	2	Frequent
51	1	m	62/30	0	1000	100	MCD	0	0	2	0	1	0	Pr	3	Frequent
52	42	f	106/59	5	1000	139	MCD	2	0	3	2	2	0	Pr + CyA	3	Frequent
53	30	m	130/80	0	1000	148	MCD	2	0	3	0	1	0	Pr	3	Normal
54	31	m	128/84	0	300	98	MCD	0	0	4	0	2	1	Pr	10	P
55	19	m	118/70	0	500	134	MCD	2	0	4	2	2	0	Pr	10	Frequent
56	18	f	126/66	0	500	170	MCD	0	0	2	0	1	0	Pr	3	Normal
57	29	f	128/66	0	300	108	MCD	0	0	2	0	1	0	Pr	3	Normal
58	19	m	116/78	0	300	124	MCD	0	0	2	0	1	0	Pr	3	Normal
59	26	m	120/60	0	300	113	MCD	0	0	3	2	1	0	Pr	5	Frequent
60	31	m	120/74	10	300	136	MCD	2	1	3	0	1	0	Pr	10	Frequent
61	62	m	136/66	5	580	73	FSGS	2	1	3	0	2	0	Pr + CyA	9	P

BP, blood pressure; Ccr, creatinine clearance; MCD, minimal change disease; PGN, mesangial proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; Pr, prednisolone; CyA, cyclosporin A; CAPD, continuous ambulatory peritoneal dialysis; CRF, chronic renal failure; Frequent, frequent relapse; HD, hemodialysis.

pared with that in asymptomatic group, but the degree of hematuria was greater in the asymptomatic group at both the biopsy and the latest follow-up compared with that in the nephrotic group. The degree of proteinuria decreased significantly in both groups between at the biopsy and at the latest follow-up. The degree of creatinine clearance was lower in the asympatomatic group at the biopsy than in the nephrotic group, but that was not different at the latest follow-up between two groups.

Nine patients in asymptomatic group (patients 3, 5, 7, 18, 19, 27, 29, 32, and 36) were treated with prednisolone because of PGN and FSGS despite mild or moderate proteinuria. All patients in the nephrotic group were treated with prednisolone and/or cyclosporine. In the asymptomatic group, 10 patients (patients 4, 12 to 18, 20, and 28) showed normal urinalysis at the latest follow-up, and persistent urinary abnormalities were evident in 24 patients. The remaining 2 patients with FSGS (patients 3 and 27) developed end-stage kidney disease 8 yr and 15 yr after the biopsy, respectively. In the nephrotic group, 8 of 25 patients (patients 40, 45, 47, 48, 53, and 56 to 58) showed normal urinalysis with prednisolone and/or cyclosporine. Three patients (patients 44, 54, and 61) showed persistent proteinuria at the latest follow-up. Thirteen patients (patients 37 to 39, 41 to 43, 49 to 52, 55, 59, and 60) were still frequent relapsers, and one child with FSGS (patient No. 46) developed end-stage kidney disease despite prednisolone treatment 10 yr after the biopsy.

One patient (patient 21) in the asymptomatic group received the second biopsy 2 yr after the biopsy because of nephrotic range-heavy proteinuria. Seven patients (patients 38, 42, 44, 48, and 50 to 52) in the nephrotic group received the second biopsy 2 to 4 yr after the first biopsy because of frequent relapsing NS. Mesangial C1q deposition disappeared in 3 patients (patients 21, 42, and 52) at the second biopsy, and two patients (patients 21 and 42) showed FSGS at the second biopsy. The remaining patients showed MCD at the second biopsy. Normal urinalysis was found in one patient (patient 48) with prednisolone and cyclosporine at the latest follow-up, and persistent proteinuria was evident in one patient (patient 44). The remaining 4 patients showed frequent relapsing NS at the latest follow-up. Four patients (patients 9, 36, 41, and 59) were retrospectively found to have received biopsy 2 to 6 yr before the enrolling of the present study. At that time, IF study revealed no deposition of immunoglobulins and complement components in these 4 patients.

Discussion

In the present study, the number of patients is more and the duration of follow-up is longer compared with those in previous reports (1–11). A large number of C1qN revealed MCD on light microscopy in both asymptomatic and nephrotic patients in the present study as well as our previous report (12). There were 3 patients showing the disappearance of C1q deposits through the follow-up period. FSGS developed in 2 of these 3 patients on repeat biopsies. There were 4 patients who showed no mesangial C1q deposition in the biopsy performed before the enrolling of the present study. In our relative long-term

Table 2. Comparison of clinical findings between asymptomatic and nephrotic patients

	Asymptomatic	Nephrotic	*P*
No. of cases	36	25	
Age (yr)	20.1 ± 16.7	18.7 ± 13.6	NS
Histologic findings at initial biopsy			
MCD	23	23	<0.025
PGN	7	0	
FSGS	6	2	
Duration between the biopsy and the latest follow-up (yr)	8.2 ± 5.1	5.4 ± 3.3	NS
Clinical findings at the biopsy			
blood pressure (mmHg)			
at the biopsy	114 ± 18/61 ± 14	112 ± 15/60 ± 13	NS
at the latest follow-up	112 ± 10/46 ± 10	116 ± 15/52 ± 8	NS
proteinuria (mg/dl)			
at the biopsy	108.0 ± 125.1	572.8 ± 468.7	<0.0001
at the latest follow-up	40.1 ± 51.1[a]	154.2 ± 121.5[b]	0.0012
hematuria (RBC/hpf)			
at the biopsy	55.9 ± 91.6	1.2 ± 3.0	<0.0001
at the latest follow-up	14.0 ± 17.2[c]	0.0 ± 0.0	0.0006
creatinine clearance (ml/min)			
at the biopsy	116.2 ± 25.9	132.6 ± 29.5	0.0341
at the latest follow-up	110.0 ± 41.1	121.6 ± 30.5	NS
clinical outcome			
normal	10 (28%)	8 (32%)	NS
hematuria + proteinuria	24 (67%)	3 (12%)	NS
frequent relapsing NS	0 (0%)	13 (52%)	NS
renal failure	2 (5%)	1 (4%)	NS

Values are mean ± SD. NS, not significant. The data were analyzed using the χ^2 test and the Mann-Whitney U test.
[a]$P = 0.0017$, at the biopsy *versus* at the latest follow-up in the asymptomatic group.
[b]$P < 0.0001$, at the biopsy *versus* at the latest follow-up in the nephrotic group.
[c]$P = 0.0138$, at the biopsy *versus* at the latest follow-up in the asymptomatic group.

follow-up, the prognosis of C1qN is good in both asymptomatic and nephrotic patients.

Previous reports described that urinary findings in patients with C1qN were heavy proteinuria or nephrotic range proteinuria with or without hematuria (1,3–5,9–11). In our current study as well as our previous report (12), patients with C1qN were detected as having mild to nephrotic range proteinuria. In contrast to our results, MCD was in 8 cases and FSGS in 7 in pediatric 15 cases of Iskandar *et al.* (4). Markowitz *et al.* (9) reported that FSGS was in 17 patients and MCD in 2. In our study, the prevalence of FSGS was smaller in number as compared with the results of Iskandar *et al.* (4) and Markowitz *et al.* (9). The difference between our and their results may be due to the difference of the number of examined subjects and race. In Japan, patients with asymptomatic urinary abnormalities have been detected by annual urine screening of schoolchildren. We performed renal biopsy widely in those with mild proteinuria to nephrotic range proteinuria, whereas most patients reported by Iskandar *et al.* (4) and Markowitz *et al.* (9) had nephrotic range proteinuria with hypertension or renal insufficiency. Therefore, the selection of patients with C1qN may be biased in their studies. Our patients may be detected in the early stage of C1qN.

The degree of proteinuria and hematuria improved in both asymptomatic and nephrotic groups with prednisolone and/or cyclosporine treatment through the follow-up. Normal urinalysis was evident in 10 patients in the asymptomatic group and in 8 in the nephrotic group through the follow-up. However, 13 patients in the nephrotic group were still frequent relapsers at the latest follow-up. Three patients with FSGS (2 in the asymptomatic group and one in the nephrotic group) showed chronic renal failure despite prednisolone treatment. In our study, only 3 of 61 (5%) showed chronic renal failure 8 to 15 yr after the diagnosis. The remaining patients had normal urinalysis or persistent urinary abnormalities with normal renal function at the latest follow-up. In our relative long-term follow-up (a mean follow-up period of 7.2 yr), the prognosis of C1qN appears to be good. The reason of a better prognosis in our patients is considered to be associated with MCD in a larger number of patients compared with those of Iskandar *et al.* (4) and Markowitz *et al.* (9).

There are some unresolved issues concerning C1qN. The first

question is that the prevalence of this disease is lower compared with the prevalence of IgA glomerulonephritis in 18% to 40% of all primary glomerular diseases (19). The prevalence of C1qN is 0.21% to 4% (1–12). In our patients, the prevalence of C1qN was 0.4% in renal biopsies, including primary and secondary glomerular diseases. The prevalence of C1qN is about 0.8%, even in primary glomerular diseases (our laboratory's unpublished data between 1975 and 2004). The second question is that a large number of histologic findings show MCD in our patients. C1q is the first component of the classical complement pathway by binding to the Fc region of IgG and IgM after their union with antigen. It is not surprising that IgG is deposited in approximately 60% of C1qN patients. However, no remarkable mesangial proliferation is found in a large number of our patients. IgA glomerulonephritis shows a wide spectrum of morphologic findings from MCD to diffuse mesangial proliferation with or without sclerotic glomeruli (19). There are some patients with IgA glomerulonephritis in whom mesangial IgA deposits disappeared through the follow-up. Urinalysis improved in these patients with the disappearance of mesangial IgA deposits (19). Some patients with IgA glomerulonephritis were reported to have lipoid nephrosis with dominant mesangial IgA deposition on IF and mesangial EDD on EM (20,21). This group is considered to be a variant of IgA glomerulonephritis with overlapping syndrome of lipoid nephrosis (20,21). In 3 of 8 patients receiving repeat biopsy, C1q deposits disappeared at the time of the second biopsy. However, histologic findings and urinalysis were worsened in these 3 patients despite disappearance of C1q deposits. The pathogenesis of C1qN is likely to be different from IgA glomerulonephritis in view of the disappearance of mesangial deposits. Furthermore, in our current study, 4 patients were retrospectively found to have showed no mesangial deposits of C1q in the biopsy performed before the enrolling of the present study. These results suggest that C1qN may be overlapping or superimposing with MCD, mesangial proliferative glomerulonephritis, or FSGS. C1q immune complex may by chance deposited in the mesangial area in underlining diseases of MCD, mesangial proliferative glomerulonephritis, or FSGS. However, from the results of our current study, we could not completely clarify whether C1qN was a distinct clinical entity or C1qN was overlapping with the other glomerulonephritides.

Conclusion

C1qN is found in patients with a wide clinical and a wide histologic spectrum. A large number of C1qN show MCD in asymptomatic and symptomatic patients. In our relative long-term follow-up, the prognosis of C1qN is good. There are some patients showing the disappearance of C1q deposits through the follow-up period. FSGS may develop in some patients with time. Further investigation is critically needed to settle this issue.

Disclosures

None.

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REVIEW ARTICLE

Anti-glomerular basement membrane antibody disease in Japan: part of the nationwide rapidly progressive glomerulonephritis survey in Japan

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Abstract Anti-glomerular basement membrane (anti-GBM) antibody disease is a rare, but well characterized cause of glomerulonephritis. It is defined by the presence of autoantibodies directed at specific antigenic targets within the glomerular basement membrane. This pattern of rapidly progressive glomerulonephritis and alveolar hemorrhage is often referred to as Goodpasture's syndrome. The prognosis for patients with anti-GBM antibody disease is poor. In Japan, to improve the prognosis of patients with rapidly progressive glomerulonephritis (RPGN), we conducted a nationwide survey of patients with RPGN and investigated the initial symptoms, laboratory findings including renal biopsy findings, treatment methods, and outcomes. Among patients with RPGN, patients with anti-GBM antibody disease were rare: 6.6% (47/715). Alveolar hemorrhage (Goodpasture's syndrome) was observed in 23.4% of patients with anti-GBM antibody disease. Most patients with anti-GBM antibody disease had renal failure at the time of diagnosis. The mean serum creatinine level of patients with renal-limited anti-GBM antibody disease was 7.07 ± 4.21 mg/dl and that of patients with Goodpasture's syndrome was 7.99 ± 4.31 mg/dl. The mean level of crescent formation was 78.99 ± 23.54% in patients with anti-GBM antibody disease, and a cellular crescent form was observed in 63.2% of those patients. The prognosis for patients with anti-GBM antibody disease is poor; the renal survival rate at 6 months after onset was 20.9%, and the mortality at 6 months after onset was 23.3%. To improve the prognosis for anti-GBM antibody disease, it may be necessary to detect this disease in the early stages and to treat it without delay.

Keywords Anti-glomerular basement membrane antibody disease · Goodpasture's syndrome · Epidemiology · Treatment · Prognosis

Introduction

Anti–glomerular basement membrane (anti-GBM) antibody disease is a rare autoimmune disorder characterized by rapidly progressive glomerulonephritis (RPGN) with diffuse crescentic formation on renal biopsy. In 1919, Goodpasture first described the autopsy findings of an 18-year-old boy with acute renal failure and massive hemoptysis during an influenza virus infection [1], and Stanton and Tange reported nine cases with alveolar hemorrhage associated with glomerulonephritis. It was proposed that this condition be called Goodpasture's syndrome in 1958 [2]. On the other hand, the nephrotoxic serum nephritis model, first described by Masugi in 1934 [3], was induced in rats by a single injection of heterologous anti-kidney sera, and Ortega and Mellors described the staining of anti-IgG antibodies along glomerular capillary walls in rats with

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nephrotoxic nephritis in 1956 [4]. In 1964, Scheer and Grossman reported linear staining of anti-human IgG antibodies in patients with Goodpasture's syndrome, similar to what was observed in rats with nephrotoxic nephritis [5]. Lerner et al. showed that antibodies eluted from the kidneys of patients with Goodpasture's syndrome could bind to the GBM of squirrel monkeys when injected in vivo and could elicit a disease pattern similar to that of anti-GBM antibody disease [6]. Therefore, anti-GBM antibody disease is defined by the presence of autoantibodies directed at specific antigenic targets within the glomerular and/or pulmonary basement membrane.

Anti-GBM antibody disease has an estimated incidence of one case per 2 million per year in European Caucasoid populations [7]. It is responsible for 1 to 5% of all types of antibody-induced glomerulonephritis [8] and is the cause of 10 to 20% of cases of crescentic glomerulonephritis [9, 10]. The disease occurs across all racial groups, but is most common in European Caucasoids. In Japan, to improve the prognosis of patients with RPGN, we conducted a nationwide survey of patients with RPGN in 365 hospitals between 1989 and 2000, and investigated the initial symptoms, laboratory findings, including renal biopsy findings, treatment methods, and outcomes [11]. In this review, the part of this nationwide survey of patients with RPGN that pertains to anti-GBM antibody disease is reported.

Epidemiological investigation

RPGN is defined by the World Health Organization as an abrupt or insidious onset of hematuria, proteinuria, anemia, and rapidly progressing renal failure [12]. In this nationwide survey, subjects who had rapid deterioration of renal function within several weeks and showed hematuria, proteinuria, and/or cellular casts upon urinalysis were regarded as patients with RPGN. Anti-GBM antibody disease was defined as the presence of serum anti-GBM antibody or a linear binding of IgG as detected by direct immunofluorescence (IF) in patients with RPGN. RPGN patients with anti-GBM antibody disease were divided into two types: anti-GBM antibody disease without alveolar hemorrhage was regarded as renal-limited anti-GBM antibody disease and that with alveolar hemorrhage was defined as Goodpasture's syndrome.

Based on this nationwide RPGN survey in Japan, 715 patients with RPGN were registered [11]. The most frequent primary disease was primary pauci-immune crescentic glomerulonephritis ($n = 283$, 39.6%; median age: 65; age range: 6–91); the second most frequent was microscopic polyangiitis (MPA; $n = 127$, 17.8%; median age: 68; age range: 5 to 91), and the third most frequent was anti-GBM antibody disease ($n = 47$, 6.6%). Among the subjects with anti-GBM antibody disease, those with alveolar hemorrhage (Goodpasture's syndrome) made up 1.5% of the RPGN patients in Japan. In comparison with foreign countries, the Japanese rate of anti-GBM antibody disease in RPGN was the lowest; Couser reported that 20% of the RPGN patients had anti-GBM antibody in the USA [9]. Anaganco et al. reported that the proportion of anti-GBM-associated RPGN in Europe was 12% [13], and Jennette reported that 15% of the RPGN patients had anti-GBM antibody [14].

All age groups are affected, but the peak incidence of anti-GBM antibody disease is in the 3rd decade in young men, with a second peak in the 6th and 7th decades affecting men and women equally [7, 15, 16]. Alveolar hemorrhage is more common in younger men, while isolated renal disease is more frequent in the elderly with a near-equal gender distribution. In this survey, the mean age at onset of renal-limited anti-GBM antibody disease was 52.6 ± 17.0 years and that for Goodpasture's syndrome was 49.4 ± 14.4 years. There was only one peak incidence of anti-GBM antibody disease in the 5th and 6th decades (Fig. 1). In comparison with MPA, the age at onset of anti-GBM antibody disease was younger; the mean age at onset of primary pauci-immune crescentic glomerulonephritis was 61.3 ± 15.8 years, and the mean age at onset of MPA was 65.6 ± 11.1 years. The gender distribution was nearly equal in renal-limited anti-GBM antibody disease (male:female = 1:0.94), but Goodpasture's syndrome was more common in females (male:female = 1:1.75).

Clinical symptoms

General malaise, weight loss, fever, or arthralgia may be the initial features of anti-GBM antibody disease in a

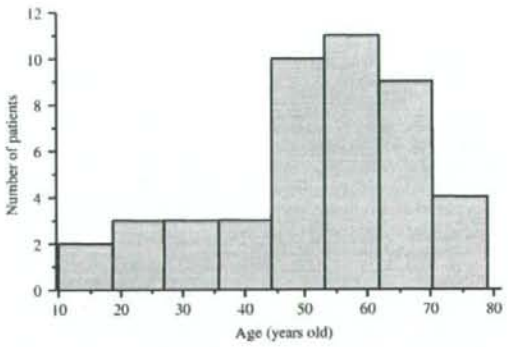

Fig. 1 The age distribution of patients with anti-GBM antibody disease in Japan. The histogram shows the number of patients with anti-GBM antibody disease classified by the patient's age at the onset of this disease

pattern similar to, but much less prominent than in systemic vasculitis. Symptoms relating to anemia may also occur even in the absence of significant hemoptysis. The principal clinical features relate to the development of renal failure due to RPGN or alveolar hemorrhage. In this survey, hemodialysis therapy had already been initiated in 59.6% (28/47) of the anti-GBM patients before the start of immunosuppressive treatments. Although one-third to two-thirds of patients with anti-GBM antibody disease demonstrate alveolar hemorrhage in general, in this survey 23.4% (11/47) of patients with anti-GBM antibody disease suffered from alveolar hemorrhage.

Laboratory examinations

Upon urinalysis, all patients with anti-GBM antibody disease had microscopic hematuria. Proteinuria is modest, but can be heavier when the disease has a more subacute course. In this survey, the mean 24-h excretion of urinary protein in renal-limited anti-GBM antibody disease was 2.1 ± 3.0 g and that of Goodpasture's syndrome was 3.7 ± 3.2 g (Table 1). Unfortunately, most patients with anti-GBM antibody disease had renal failure at the time of diagnosis, and the mean serum creatinine (s-Cr) level in renal-limited anti-GBM antibody disease was 7.07 ± 4.21 mg/dl, while that in Goodpasture's syndrome was 7.99 ± 4.31 mg/dl. Anemia was observed in most patients with anti-GBM antibody disease, and the mean hemoglobin concentration in renal-limited anti-GBM antibody disease was 8.8 ± 1.7 g/dl, while that in Goodpasture's syndrome was 7.5 ± 1.1 g/dl. The mean erythrocyte sedimentation rate (ESR) in renal-limited anti-GBM antibody disease was 105 ± 44 mm/h, and that in Goodpasture's syndrome was 82 ± 45 mm/h. The mean serum C-reactive protein (CRP) level in renal-limited anti-GBM antibody disease was 8.5 ± 7.2 mg/dl and that in Goodpasture's syndrome was 8.2 ± 8.1 mg/dl. In

Table 1 Characteristics of anti–glomerular basement membrane antibody disease in Japan

	Anti-GBM antibody disease		Microscopic polyangiitis ($n = 127$)	Wegener's granulomatosis ($n = 18$)
	Renal-limited ($n = 36$)	Goodpasture's syndrome ($n = 11$)		
Age (years)	52.6 ± 17.0	49.4 ± 14.4	65.6 ± 11.1	44.1 ± 15.5
Sex (M:F)	19:17	4:7	53:66	9:8
Urinalysis				
Proteinuria (g/day)	2.1 ± 3.0	3.7 ± 3.2	1.9 ± 3.1	0.8 ± 0.5
Hematuria	100 (26/26)	100 (10/10)	97.5 (118/121)	100 (14/14)
Blood cell counts				
WBC (/μl)	8,805 ± 3,609	10,436 ± 3,448	11,547 ± 4,880	9,431 ± 4,082
Hemoglobin (g/dl)	8.8 ± 1.7	7.5 ± 1.1	8.3 ± 1.7	9.2 ± 1.9
Platelet ($\times 10^4$/μl)	33.6 ± 12.8	29.4 ± 17.0	32.7 ± 13.6	35.9 ± 19.4
Chemistry				
Total protein (g/dl)	6.39 ± 1.14	6.43 ± 1.21	6.54 ± 0.84	6.64 ± 1.06
Albumin (g/dl)	2.94 ± 0.75	2.78 ± 0.51	2.83 ± 0.56	3.10 ± 0.39
Urea nitrogen (mg/dl)	55.9 ± 30.4	59.9 ± 26.5	50.8 ± 29.1	35.9 ± 26.3
Creatinine (mg/dl)	7.07 ± 4.21	7.99 ± 4.31	4.54 ± 3.13	3.84 ± 3.24
ESR (mm/h)	105 ± 44	82 ± 45	95 ± 40	92 ± 28
Serology				
CRP (mg/dl)	8.5 ± 7.2	8.2 ± 8.1	8.8 ± 7.9	9.6 ± 11.1
ANA (%)	11.8 (4/34)	27.3 (3/11)	36.8 (46/125)	11.8 (2/17)
A-DNA (%)	0 (0/34)	22.2 (2/9)	6.6 (7/106)	0 (0/16)
A-GBM (%)	100 (32/32)	100 (11/11)	1.2 (1/83)	0 (0/11)
MPO-ANCA (%)	10.3 (3/29)	20.0 (2/10)	95.5 (105/110)	18.8 (3/16)
PR3-ANCA (%)	0 (0/29)	10.0 (1/10)	3.6 (4/110)	68.8 (11/16)
Kidney size by abdominal US/CT				
Atrophy (%)	9.7 (3/31)	20.0 (2/10)	8.5 (10/118)	16.7 (3/18)
Swelling (%)	35.5 (11/31)	0 (0/10)	19.5 (23/118)	16.7 (3/18)
Normal (%)	54.8 (17/31)	80.0 (8/10)	72.0 (85/118)	66.7 (12/18)

Anti-GBM anti-glomerular basement membrane, *WBC* white blood cell, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* anti-nuclear antibody, *A-DNA* anti-DNA antibody, *A-GBM* anti-glomerular basement membrane antibody, *MPO* myeloperoxidase, *ANCA* anti-neutrophil cytoplasmic antibody, *PR3* proteinase-3, *US* ultrasonography, *CT* computed tomography

comparison with other forms of RPGN, such as MPA and Wegener's granulomatosis (WG), there was no difference in inflammation markers, such as leukocyte count, ESR, and serum CRP. However, in patients with anti-GBM antibody disease, the mean level of s-Cr at the time of diagnosis was higher than that in patients with MPA (4.54 ± 3.13 mg/dl) or WG (3.84 ± 3.24 mg/dl). Therefore, early diagnosis of anti-GBM antibody disease is very important.

The diagnosis of anti-GBM antibody disease is dependent on the detection of anti-GBM antibodies either in the circulation or in kidney tissue. These serum antibodies are usually detected using an enzyme-linked immunosorbent assay or radioimmunoassay method. The antibodies have not been reported to occur in the absence of disease, and false negatives are rare when appropriate checks are performed. In this survey, 91.5% (43/47) of patients with anti-GBM antibody disease were diagnosed via the detection of serum anti-GBM antibodies. In serological examinations, other autoantibodies were not usually detected. However, in this survey, anti-nuclear antibodies were detected in 11.8% of renal-limited anti-GBM antibody disease and in 27.3% of patients with Goodpasture's syndrome. Anti-DNA antibody was not detected in renal-limited anti-GBM antibody disease, but it was detected in 22.2% of patients with Goodpasture's syndrome. Moreover, anti-neutrophil cytoplasmic antibodies (ANCA) were detected in 12.8% (5/39) of patients with anti-GBM antibody disease; a perinuclear pattern was detected in all five anti-GBM antibody disease patients with ANCA, and a cytoplasmic pattern was detected in one. The coexistence of anti-GBM antibody and ANCA occurred in 15-50% of cases of anti-GBM antibody disease described in the previous literature [17–21]. In addition, previous studies revealed that patients with double-positive antibodies were MPO-ANCA predominant, older, and male predominant [17–20]. In this survey, the age at onset of patients with double-positive antibodies was higher (the mean age was 52.6 years), but female dominant (male:female = 1:4). The prognosis of patients with double-positive antibodies varied; the renal and patient survivals of patients with double-positive antibodies were reported to be better [17–18], not significantly different [19], or worse [20–21] than those of patients with anti-GBM antibody alone. In this survey, the prognosis of patients with double-positive antibodies was poor; two of them died, and the remaining three patients required maintenance hemodialysis. Alveolar hemorrhage was observed in two of five patients with double-positive antibodies, and three of them had interstitial pneumonitis.

Kidney sizes were usually normal or enlarged due to inflammation. In this survey, ultrasonography showed that 61.0% of patients with anti-GBM antibody disease had kidneys of normal size, while atrophic kidneys were observed in 12.2% of patients, and enlarged kidneys were observed in 26.8%.

Histopathological findings

A renal biopsy is essential in suspected anti-GBM antibody disease to confirm the diagnosis and to assess the renal prognosis. The histological pattern of disease starts with mesangial expansion and hypercellularity and progresses to focal and segmental glomerulonephritis with infiltration by leukocytes accompanied by segmental necrosis with prominent breaks in the GBM. Later, glomeruli develop an extensive crescent formation composed of parietal epithelial cells and macrophages in association with the destruction of the GBM. In this survey, renal biopsy or autopsy was performed in 40 of 47 patients with anti-GBM antibody disease; 2 of these patients were excluded from the analysis of glomerular lesions because their renal specimens included 5 or fewer glomeruli (Table 2). The mean percentage of glomeruli showing crescent formation was 78.99 ± 23.54% in patients with anti-GBM antibody disease. The mean percentage of glomeruli showing crescent formation in patients with anti-GBM antibody disease was significantly higher than that in MPA, another form of RPGN. The percentage of patients with anti-GBM antibody disease who had more than 50% crescentic glomeruli was 89.5% (34/38). Crescent patterns are usually divided into three groups: cellular, fibrocellular, or fibrous crescents. In 63.2% of anti-GBM antibody disease, the most dominant crescent pattern was cellular. The percentage of patients with cellular crescentic glomeruli in anti-GBM antibody disease was higher than in MPA and WG.

Interstitial inflammation is usually present and may relate to the binding of antibodies to the basement membrane of distal convoluted tubules. In this survey, severe tubulointerstitial damage was present in 45.0% of cases of anti-GBM antibody disease, and moderate damage was present in 40.0%.

Linear binding of IgG is universally detected by direct IF. Linear C3 is found in 60 to 70% of kidney biopsies, but does not influence the severity of the renal lesion [22].

Pulmonary lesions are usually observed to be hemorrhages, with numerous hemosiderin-containing macrophages, deposits of fibrin and alveolar cell hyperplasia, histologically. Necrosis of alveolar walls with polymorphonuclear cell infiltration is also recognized. On IF examination, linear binding of IgG is usually detected along the alveolar basement membrane. In this survey, histopathological data of pulmonary lesions were not accumulated.

Table 2 The histologic pattern of anti-glomerular basement membrane antibody disease in Japan

		Anti-GBM antibody disease ($n = 40$)	Microscopic polyangiitis ($n = 103$)	Wegener's granulomatosis ($n = 18$)
Percentage of patients with adequate specimens		100 (40/40)	98.1 (101/103)	94.4 (17/18)
Percentage of patients with more than five glomeruli		95.0 (38/40)	91.3 (94/103)	77.8 (14/18)
Mean number of glomeruli		21.53 ± 12.87	21.28 ± 14.12	22.47 ± 20.62
Mean percentage of glomeruli showing crescent formation		78.99 ± 23.54	58.74 ± 27.66	76.76 ± 20.90
Percentage of patients with more than 50% crescentic glomeruli		89.5 (34/38)	60.6 (57/94)	78.6 (11/14)
Most dominant crescent pattern (%)	Cellular	63.2 (24/38)	50.0 (47/94)	35.7 (5/14)
	Fibrocellular	21.1 (8/38)	37.2 (35/94)	42.9 (6/14)
	Fibrous	15.8 (6/38)	9.6 (9/94)	21.4 (3/14)
Percentage of patients with vasculitis		5.0 (2/40)	46.5 (54/101)	0 (0/17)
Grade of tubulointerstitial damage (%)	None	7.5 (3/40)	2.0 (2/101)	11.8 (2/17)
	Mild	7.5 (3/40)	9.9 (10/101)	11.8 (2/17)
	Moderate	40.0 (16/40)	48.5 (49/101)	52.9 (9/17)
	Severe	45.0 (18/40)	39.6 (40/101)	23.5 (4/17)

Anti-GBM anti–glomerular basement membrane

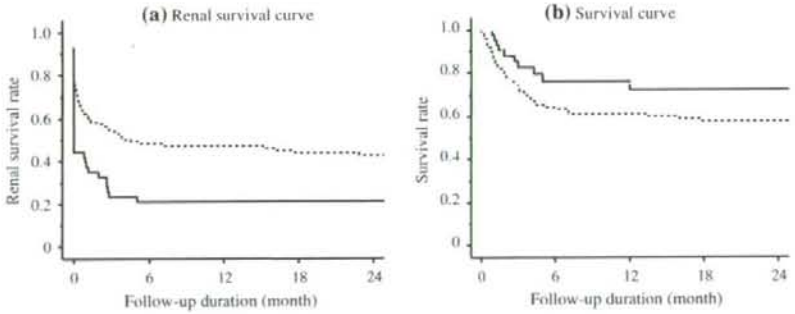

Fig. 2 The survival curves in patients with anti–GBM disease in Japan. The patients' renal survival curve (Kaplan-Meier method) is shown on the left (**a**), and their survival curve is shown on the right (**b**). The *straight line* is the survival curve of patients with anti–GBM antibody disease, the *dotted line* is the survival curve of patients with microscopic polyangiitis, and the *shaded line* is the survival curve of patients with Wegener's granulomatosis

Treatments and prognosis

Without treatment, the prognosis for patients with anti-GBM antibody disease is poor. In this survey, 4 of 47 patients with anti-GBM antibody disease had an undefined clinical course, and the mean follow-up period was 20.3 ± 24.3 months. Excluding the above four patients, the renal survival rate at 6 months after onset was 20.9% (9/43), but the mortality rate at 6 months after onset was 23.3% (10/43, Fig. 2). In comparison with MPA and WG, there was no difference in the survival rate, but the renal survival rate of anti-GBM antibody disease was significantly lower ($P < 0.001$ by the Logrank Mantel-Cox test). Wilson and Dixon reported that 25 of 53 patients died, and only 7 retained independent renal function [8]. It appeared that neither corticosteroids nor immunosuppressive agents had an influence on the renal outcome. However, it is difficult to normalize circulating anti-GBM antibody titers in the short term by the combination therapy of corticosteroids and immunosuppressive agents alone. The demonstration that anti-GBM antibodies were pathogenic provided a rationale for the current approach to treatment using therapeutic plasma exchange combined with immunosuppressive agents. The effectiveness of this therapeutic approach for improving renal function has been reported (Table 3). Renal function improves in 15–75% of patients

Table 3 Previous investigations of treatments for anti-glomerular basement membrane antibody disease

Authors	Ref. No.	Year	Treatment	*N*	Alveolar hemorrhage (%)	1 year (%)	
						Patient survival	Renal survival
Benoit et al.	[23]	1963	No treatment	52	100	4	2
Proskey et al.	[24]	1970	IS	56	100	77	23
Wilson and Dixon	[8]	1973	IS	53	60	53	13
Beirne et al.	[25]	1977	IS	29	54	42	17
Teague et al.	[26]	1978	IS + PE	29	100	64	31
Briggs et al.	[27]	1979	IS	18	61	84	22
Peters et al.	[28]	1982	IS + PE	41	56	76	39
Walker et al.	[29]	1985	IS + PE	22	62	59	45
Savage et al.	[30]	1986	IS + PE	108	52	78	20
Johnson et al.	[31]	1986	OCS + CYC	9	NA	89	22
			OCS + CYC + PE	8	NA	100	75
Herody et al.	[32]	1993	OCS + CYC + AZA	29	50	93	41
Merkel et al.	[16]	1994	OCS + CYC + PE	35	57	89	29
Daly et al.	[33]	1996	IS + PE	40	67	NA	20
Li et al.	[34]	2004	IS + PE	10	40	70	15
Cui et al.	[35]	2005	IS + PE	97	58	92	22

Ref reference, *N* number of patients, *IS* immunosuppressants (including methylprednisolone pulse therapy, oral corticosteroids, cyclophosphamide or azathioprine), *PE* plasma exchange, *OCS* oral corticosteroids, *CYC* cyclophosphamide, *AZA* azathioprine, *NA* not available

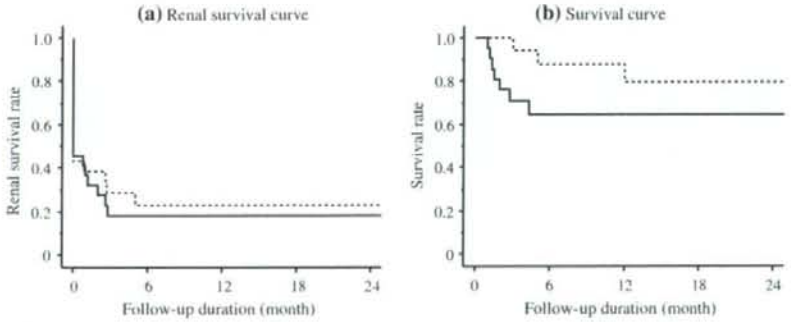

Fig. 3 The survival curves of patients with anti-GBM antibody disease: Difference between the presence and absence of plasma exchange. The patients' renal survival curve (Kaplan-Meier method) is shown on the left (**a**), and their survival curve is shown on the right (**b**). The *straight line* is the survival curve of anti-GBM antibody disease patients treated with plasma exchange, and the *dotted line* is the survival curve of those treated without plasma exchange

with anti-GBM antibody disease through the combination of plasma exchange with corticosteroids and immunosuppressive agents, while the renal survival rates of anti-GBM antibody disease patients treated with immunosuppressive agents alone ranged from 2–22% [7, 8, 16, 23–35]. Improvement of renal function is usually evident within days of the start of plasma exchange. However, it should be emphasized that the regimen has never been properly assessed by a prospective randomized controlled trial because of the rarity and acuteness of the condition. The only reported randomized controlled trial was very small and used lower doses of both plasma exchange and cyclophosphamide than those that are used generally [31].

In this survey, 55.3% (26/47) of patients with anti-GBM antibody disease were treated with plasma exchange. However, there was no significant difference in the renal survival rate between anti-GBM antibody disease patients treated with and without plasma exchange ($P = 0.683$ by the log-rank Mantel-Cox test, Fig. 3a). Moreover, there was no significant difference in mortality between anti-GBM antibody disease patients treated with and without plasma exchange ($P = 0.109$, Fig. 3b). Renal function

Table 4 Numbers of patients with end-stage renal failure or death among patients with anti–glomerular basement membrane antibody disease: a comparison of various treatments

Prognosis		ESRD or death				Death			
Plasma exchange		Absent		Present		Absent		Present	
OCS	Absent	100%	(5/5)	100%	(2/2)	0%	(0/5)	0%	(0/2)
	Present	68.8%	(11/16)	80.0%	(16/20)	18.8%	(3/16)	35.0%	(7/20)
MP	Absent	100%	(6/6)	100%	(4/4)	16.7%	(1/6)	0%	(0/4)
	Present	66.7%	(10/15)	77.8%	(14/18)	13.3%	(2/15)	38.9%	(7/18)
CYC	Absent	77.8%	(14/18)	83.3%	(10/12)	5.6%	(1/18)	16.7%	(2/12)
	Present	66.7%	(2/3)	80.0%	(8/10)	66.7%	(2/3)	50.0%	(5/10)
IVCY	Absent	75.0%	(15/20)	80.0%	(16/20)	10.0%	(2/20)	35.0%	(7/20)
	Present	100%	(1/1)	100%	(2/2)	100%	(1/1)	0%	(0/2)
Total		76.2%	(16/21)	81.8%	(18/22)	14.3%	(3/21)	31.8%	(7/22)

ESRD end-stage renal disease, *OCS* oral corticosteroids, *MP* methylprednisolone pulse therapy, *CYC* cyclophosphamide, *IVCY* intravenous cyclophosphamide

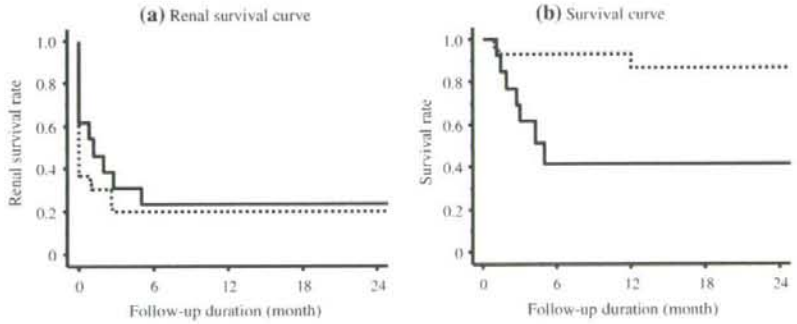

Fig. 4 The survival and renal survival rates in patients with anti–GBM antibody disease: Difference between the presence and absence of cyclophosphamide. The patients' renal survival curve (Kaplan-Meier method) is shown on the left (**a**), and their survival curve is shown on the right (**b**). The *straight line* is the survival curve of anti–GBM antibody disease patients treated with cyclophosphamide, and the *dotted line* is the survival curve of those treated without cyclophosphamide

improves coincident with the introduction of plasma exchange in about 80% of patients with a s-Cr less than or equal to 6.8 mg/dl (600 μmol/l), but in far fewer of those with higher s-Cr levels or those who require dialysis [36]. This result may suggest that in patients with a s-Cr level over 6.8 mg/dl (600 μmol/l) and an absence of alveolar hemorrhage, the benefits of treatment are outweighed by the risks [37]. There have been a number of anecdotal reports of recovery in such patients [30, 38, 39] who usually have a short history with rapidly declining renal function and who usually show a recent onset of the disease with possibly extensive crescent formation without evidence of scarring on renal biopsy. In this survey, unfortunately, 72.3% (34/47) of patients with anti-GBM antibody disease had s-Cr levels higher than 6 mg/dl at the time of diagnosis, and the mean percentage of crescent formation was high in anti-GBM antibody disease patients. Therefore, in most patients with anti-GBM antibody disease in this survey, the time of diagnosis may have been too late to improve the renal function by combination therapy. Although the efficacy of this regimen of therapeutic plasma exchange and immunosuppressive agents was not confirmed in this survey, aggressive treatment may sometimes be justified in particular cases, even in the presence of severe renal failure.

Alveolar hemorrhage is usually responsive to treatment with this regimen and may even respond to the injection of methylprednisolone [40]. As an immunosuppressive therapy, 85.1% (40/47) of patients with anti-GBM antibody disease were treated with oral corticosteroids, 78.7% (37/47) were treated with methylprednisolone pulse therapy, 29.8% (14/47) were treated with oral cyclophosphamide, and 6.4% (3/47) were treated with intravenous cyclophosphamide (IVCY) therapy. Excluding four patients with

unknown outcomes, the final outcome of each treatment is shown in Table 4. Although there was no significant difference in the renal survival rate between anti-GBM antibody disease patients treated with and without cyclophosphamide ($P = 0.495$, Fig. 4a), the survival rate of anti-GBM antibody disease patients treated with cyclophosphamide was significantly lower than that of anti-GBM antibody disease patients treated without cyclophosphamide ($P = 0.003$, Fig. 4b). However, in anti-GBM antibody disease patients treated with cyclophosphamide, the percentage with alveolar hemorrhage was significantly higher than in those treated without cyclophosphamide (50.0% vs. 14.3%, $P = 0.02$). Moreover, the mean dose of oral corticosteroids in anti-GBM antibody disease patients treated with cyclophosphamide was higher (0.96 ± 0.25 mg/kg/day vs. 0.76 ± 0.23 mg/kg/day, $P = 0.07$) than that in anti-GBM antibody disease patients treated without cyclophosphamide. In addition, the operation rate of plasma exchange in anti-GBM antibody disease patients treated with cyclophosphamide was significantly higher than that in patients treated without cyclophosphamide (85.7% vs. 52.4%, $P = 0.04$). Therefore, in this survey, the condition of the anti-GBM antibody disease patients treated with cyclophosphamide may have been more severe than that of the patients treated without cyclophosphamide, resulting in a poor survival rate. On the other hand, the renal survival of the patients treated with cyclophosphamide was not poor, regardless of their poor survival rate. Considering the results of this survey and those described in the previous literature, we can conclude that cyclophosphamide may be a useful immunosuppressive therapy even considering its adverse effects.

Relapse or recurrence of anti-GBM antibody disease with antibody production has been reported, but is quite rare. Recurrences may occur many years after the initial presentation with or without evidence of either renal or pulmonary disease [41–44]. These episodes may occur spontaneously or may be precipitated by infection or exposure to a toxic agent. In this survey, relapse or recurrence was also rare in patients with anti-GBM antibody disease (13.9%) in comparison with patients with ANCA-associated vasculitis, such as WG (29.4%) and MPA (29.3%). Therefore, remission induction therapy is more important in anti-GBM antibody disease.

Conclusion

In the nationwide RPGN survey in Japan, the incidence of anti-GBM antibody disease in RPGN was not high. However, most patients with anti-GBM antibody disease unfortunately had renal failure and had a high percentage of crescent formation at the time of diagnosis. Consequently, in most patients with anti-GBM antibody disease, it may already be too late at the time of diagnosis to perform the combination therapy of therapeutic plasma exchange and immunosuppressive agents, resulting in poor renal survival. Thus, it is important to detect anti-GBM antibody disease in the early stages and to treat it without delay.

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特集　血管炎の診療に役立つ新たな知見

難治性Wegenerにおけるリツキシマブの効果*

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臼井丈一**

Key Words：rituximab, Wegener's granulomatosis, PR3-ANCA, RPGN

はじめに

Wegener肉芽腫症の標準的治療として，副腎皮質ステロイド薬とシクロホスファミドとの併用療法が確立している．しかし，この標準的治療プロトコールでは寛解導入できなかったり，副作用により治療継続が困難となる治療抵抗症例や治療薬の減量に伴う再発症例などの難治性症例が20%程度存在することが知られており，標準的治療に替わる新たな治療法の早急な確立が切望されている．これらの難治性症例では，上下気道，腎臓といった主病変以外に，脳血管病変，髄膜炎，肥厚性硬膜炎，多発単神経炎，心血管病変，眼窩内病変などの多彩な臓器病変が認められる症例が多い．

リツキシマブ(rituximab，商品名：リツキサン，Rituxan®)はヒトIgG1κの定常部とIgG1型マウス抗CD20抗体重鎖および軽鎖の可変部を融合してキメラ化したモノクローナル抗体である．抗体定常部をヒト化したことによりヒト補体に対する感受性は増強しており，抗体がCD20陽性Bリンパ球に結合すると，complement dependent cytotoxicity(CDC)およびantibody-dependent cell-mediated cytotoxicity(ADCC)により標的Bリンパ球はアポトーシスに陥る．そのため，末梢血液中からBリンパ球を消失させることが可能となる．保険適応上はB細胞性非ホジキンリンパ腫に対する治療薬であるが，近年では，血液型不適合腎移植，液性拒絶型移植腎拒絶反応，関節リウマチ，全身性エリテマトーデス，シェーグレン症候群，筋炎，自己免疫性溶血性貧血，血栓性血小板減少性紫斑病などへの有効性が報告されている．とくに関節リウマチ，全身性エリテマトーデスに対しては欧米を中心に臨床試験が施行され，いずれも良好な成績が得られている[1)2)]．難治性血管炎症候群もその適応疾患となりうることが報告されており，とくに欧米では標準的治療が確立しているWegener肉芽腫症の難治症例に対する新たな治療薬として注目されている．

本邦における難治性Wegener肉芽腫症の現状

厚生労働省「進行性腎障害」研究班急速進行性糸球体腎炎(rapidly progressive glomerulonephritis；以下RPGN)分科会(分科会長・筑波大学山縣邦弘)では1996年度から本邦におけるRPGNの現状の把握と診療指針作成ならびにデータベース構築を目的として全国個別アンケート調査を実施し，現在までに1,773例のデータを集積し，解析を行ってきた．わが国の症例では抗

* Rituximab for refractory/relapsing Wegener's granulomatosis.

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表1　RPGN症例におけるANCA陽性頻度

		P+ C+		P+ C−		P− C+		P− C−	
		症例数	%	症例数	%	症例数	%	症例数	%
一次性	半月体形成性糸球体腎炎								
	抗GBM抗体型半月体形成性糸球体腎炎	1	1.41%	6	8.45%	2	2.82%	62	87.32%
	免疫複合体型半月体形成性糸球体腎炎	0	0.00%	12	41.38%	3	10.34%	14	48.28%
	Pauci-immune型半月体形成性糸球体腎炎	38	5.40%	581	82.53%	14	1.99%	71	10.09%
	混合型半月体形成糸球体腎炎	0	0.00%	26	89.66%	1	3.45%	2	6.90%
	分類不能型	1	4.17%	9	37.50%	1	4.17%	13	54.17%
	半月体形成を伴う糸球体腎炎								
	膜性増殖性糸球体腎炎	0	0.00%	0	0.00%	0	0.00%	13	100.00%
	膜性腎症	0	0.00%	2	40.00%	0	0.00%	3	60.00%
	IgA腎症	0	0.00%	1	2.78%	1	2.78%	34	94.44%
	非IgA型メサンギウム増殖性糸球体腎炎	0	0.00%	1	14.29%	0	0.00%	6	85.71%
	その他の一次性糸球体腎炎	0	0.00%	1	100.00%	0	0.00%	0	0.00%
全身性	Goodpasture症候群	2	7.69%	7	26.92%	0	0.00%	17	65.38%
	全身性エリテマトーデス	0	0.00%	11	21.57%	1	1.96%	39	76.47%
	Wegener肉芽腫症	3	6.82%	7	15.91%	28	63.64%	6	13.64%
	顕微鏡的多発血管炎	13	4.17%	274	87.82%	6	1.92%	19	6.09%
	その他の壊死性血管炎	0	0.00%	9	69.23%	1	7.69%	3	23.08%
	紫斑病性腎炎	0	0.00%	2	6.06%	0	0.00%	31	93.94%
	クリオグロブリン血症	0	0.00%	2	20.00%	1	10.00%	7	70.00%
	関節リウマチ	1	4.55%	9	40.91%	2	9.09%	10	45.45%
	悪性腫瘍	0	0.00%	1	33.33%	0	0.00%	2	66.67%
	その他の全身性疾患	0	0.00%	15	48.39%	1	3.23%	15	48.39%
感染症	溶連菌感染後糸球体腎炎	0	0.00%	0	0.00%	0	0.00%	3	100.00%
	感染性心内膜炎，シャント腎炎	0	0.00%	0	0.00%	0	0.00%	4	100.00%
	C型肝炎ウイルス	0	0.00%	0	0.00%	0	0.00%	2	100.00%
	その他	0	0.00%	2	10.00%	0	0.00%	18	90.00%
薬剤性		1	10.00%	5	50.00%	0	0.00%	4	40.00%
その他		0	0.00%	3	25.00%	1	8.33%	8	66.67%
不明		2	2.56%	57	73.08%	1	1.28%	18	23.08%
全体		62	3.89%	1,043	65.47%	64	4.02%	424	26.62%

P：MPO-ANCA, C：PR3-ANCA　　（厚生労働省「進行性腎障害」研究班RPGN分科会全国アンケート調査より）

好中球細胞質抗体(anti neutrophil cytoplasmic antibody；以下ANCA)陽性症例の中で圧倒的にmyeloperoxidase-ANCA(以下MPO-ANCA)陽性例が多く，欧米と大きく異なっており，RPGN症例のうちproteinase 3-ANCA(以下PR3-ANCA)陽性例やWegener肉芽腫症は明らかに少ない(表1)．Wegener肉芽腫症の多くを含むPR3-ANCA型RPGNは69例のエントリーがあった．すでに標準的治療が確立しているPR3-ANCA型RPGNの場合，腎病変に限定すれば24か月腎生存率は80%以上であり，MPO-ANCA型や抗糸球体基底膜(glomerular basement membrane；以下GBM)抗体型RPGNと比較し良好であるものの，生命予後に関しては他のRPGNと比較し依然不良である(表2)．また，再発率に関しても，MPO-ANCA型や抗GBM抗体型RPGNと比較し高頻度であることが判明している(表3)．本研究班の全国アンケート調査からは，おそらく難治性Wegener肉芽腫症を含むと考えられるPR3-ANCA型RPGNは生命予後・再発ともに依然改善の余地があると考えられ，新たな治療薬の導入が必要であることを示唆している．

リツキシマブの有効性に関する諸外国からの報告

難治性血管炎症候群，中でも難治性Wegener肉芽腫症に対するリツキシマブの有効性はいくつかのRCTを含めて欧米より報告がある．2001

表2 RPGN症例の生命予後，腎予後の年次推移

	n	6か月生存率	12か月生存率	24か月生存率	n	6か月腎生存率	12か月腎生存率	24か月腎生存率
1998年以前								
RPGN全体	883	79.2	75.5	72	812	73.3	71.9	68.7
抗GBM抗体型	52	79.9	77.8	73.3	39	47.8	44.4	44.4
MPO-ANCA型	424	75.6	72.5	68.6	392	74.3	72.3	69.4
PR3-ANCA型	32	78.1	71.6	71.6	27	85.2	85.2	85.2
ANCA陰性pauci-immune型	46	73.7	68.9	68.9	45	69.8	69.8	66.9
SLE	50	85.9	85.9	83.8	47	89.1	86.8	84.4
免疫複合体型	27	80.2	76.2	72	24	56.7	56.7	56.7
1999～2001年								
RPGN全体	321	80.1	78.3	72.8	288	81.3	78.6	75.4
抗GBM抗体型	24	82.1	82.1	77.3	18	50	50	50
MPO-ANCA型	183	81.7	79.9	73.7	166	87.4	85	81.4
PR3-ANCA型	12	75	75	65.6	10	90	90	90
ANCA陰性pauci-immune型	30	81.5	81.5	81.5	29	92.5	92.5	92.5
SLE	5	60	60	60	4	66.7	66.7	66.7
免疫複合体型	3	66.7	66.7	66.7	3	100	100	100
2002年以降								
RPGN全体	562	86.1	82.8	77.7	411	81.8	80.5	76.7
抗GBM抗体型	30	82.8	71	71	23	46.8	46.8	41
MPO-ANCA型	385	85.9	83.2	79.3	361	85.7	83.8	79.8
PR3-ANCA型	25	71.6	71.6	59.7	22	80.5	80.5	80.5
ANCA陰性pauci-immune型	28	91.8	86.1	70.4	26	75.5	75.5	64.8
SLE	11	90	90	78.8	11	80.8	80.8	80.8
免疫複合体型	6	75	75	75	6	85.7	85.7	85.7

（厚生労働省「進行性腎障害」研究班RPGN分科会全国アンケート調査より）

表3 RPGN症例の治療経過と再発

病型	全症例数	寛解		再発		再発回数	
		回答数	寛解症例数(率%)	回答数	再発症例数(率%)	回答数	平均再発数(回数範囲)
MPO-ANCA型	996	852	297(34.9%)	847	147(17.4%)	195	1.57(0～8回)
抗GBM抗体型	106	87	23(26.4%)	95	11(11.6%)	18	1(0～1回)
PR3-ANCA型	69	55	15(27.3%)	58	15(25.9%)	15	1.67(0～3回)
全体	1,772	1,471	448(30.5%)	1,483	246(16.6%)	331	1.59(0～8回)

（厚生労働省「進行性腎障害」研究班RPGN分科会全国アンケート調査より）

年のSpecksらによる1例の有効症例報告に始まり[3]，2005年までに複数の施設よりさまざまな難治性臓器病変に対する有効症例が報告されている．2005年になると多数症例とは言えないものの，ある程度のまとまった症例数を解析した後ろ向き検討報告が散見されるようになり[4][5]，翌2006年には3つの前向き試験の結果が相次いで報告された[6]～[8]．各報告から，症例数，リツキシマブ投与プロトコール，完全寛解症例数(率)，完全寛解症例再発症例数(率)，血清ANCA値低下症例数を表4にまとめた．投与方法はリンパ腫のプロトコールとほぼ同様の投与量，投与間隔を採用している報告が多く，実際は375mg/m^{2}の週1回投与を4回で1クールとして投与している．総症例数は58例であり，一部の報告での寛解率は低いものの，全体では寛解症例数は45例(78%)とおおむね良好な成績であった．また，完全寛解に達した症例における12か月以内の再発率は13%とこちらも良好な治療効果であった．いくつかの報告で点滴時過敏反応や感染症などの副作用がみられているものの，いずれも深刻な問題にはなっていないようである．末梢血か

表4　難治性Wegener肉芽腫症に対するリツキシマブの有効性を検討した過去の報告

著者	発表国	発表年	検討方法	症例数	リツキシマブ投与方法(回×mg/m²)	寛解症例数(率%)	12か月再発数(率%)	PR3-ANCA低下症例数(率%)	参考文献
Keogh KA	アメリカ	2005	後ろ向き	11	4×375	11(100)	2(18)	11(100)	4)
Eriksson P	スウェーデン	2005	後ろ向き	7	2 or 4×500mg	6(86)	1(17)	1(14)*	5)
Keogh KA	アメリカ	2006	前向きオープン	10	4×375	10(100)	1(10)	10(100)	6)
Aries PM	ドイツ	2006	前向きオープン	8	4×375	2(25)	0(0)	2(25)	7)
Stasi R	イギリス	2006	前向きオープン	8	4×375	7(88)	1(14)	8(100)	8)
Brihaye B	フランス	2007	後ろ向き	8	7例：4×375，1例：2×1,000mg	5(63)	1(20)	6例中3(50)*	9)
Henes JC	ドイツ	2007	後ろ向き	6	4×375	4(67)	0(0)	6(100)	10)
全体				58		45(78)	6(13)		

* Immunofluorescence-ANCA

らのBリンパ球の消失に伴い，ほぼ全例で血清ANCA値が低下している．しかし，Bリンパ球の回復に伴い，血清ANCA値が再上昇し，臨床症状の再発や増悪を招くという事象が確認されている．また，腎移植後の難治性症例に対するリツキシマブの治療成功例の報告もなされており[11]，今後，さらなる使用症例の集積および解析が望まれる．

本邦での有効性に関する報告

難治性血管炎症候群に対するリツキシマブの有効性に関するわが国での報告例はいまだ少ない．Tamuraら(順天堂大学膠原病内科)は，難治性2例の有効例を発表している[12]．治療により臨床症状は消失し，検査データ上も末梢血中のBリンパ球の消失後にPR3-ANCA値の著明な低下を認めている．2例とも副腎皮質ステロイド薬を併用しているが，その減量に成功している．また，うち1例は肥厚性硬膜炎と眼窩内肉芽腫の改善例である．南ら(国立病院機構九州医療センター膠原病内科)は，多発単神経炎，多関節炎，眼窩内肉芽腫，脳梗塞，完全房室ブロックなどの多彩な臨床症状を伴った難治性再発性1例の有効例を発表している[13]．この症例においても，臨床症状は消失し，副腎皮質ステロイド薬の減量に成功している．そして，代表的難治性病変である眼窩内肉芽腫に対する有効性に関する報告もある．山田ら(聖マリアンナ医科大学内科学)は，リツキシマブにおいて改善した難治性眼窩内肉芽腫3症例を報告している[14]．大変興味深いことに，この3例はいずれの症例もリツキシマブ投与直前のPR3-ANCAがすでに陰性化しており，本病態に対するBリンパ球のPR3-ANCA非依存性の関与が示唆されている．

残念ながら，わが国からの多数症例の後ろ向き検討や前向き試験の報告はいまだなされていないが，厚生労働省「難治性血管炎研究」班(班長・聖マリアンナ医科大学尾崎承一)において難治性Wegener肉芽腫症を含む難治性ANCA関連血管炎に対するリツキシマブの有効性を検討する前向きコホート研究が現在進行中である．2006年度研究報告にみる経過報告[15]では，登録された7症例のうち5症例がWegener肉芽腫症であり，公表されている観察期間は2～9か月と短期間なものの，4例で症状の改善(寛解3例，部分寛解1例)が確認されている．今後，本研究は厚生労働省「ANCA関連血管炎のわが国における治療法の確立のための多施設共同前向き臨床研究」班に引き継がれ，追加観察の結果が公表される予定であり，その成果が期待される．

おわりに

難治性Wegener肉芽腫症におけるリツキシマブの至適な投与量，投与回数，投与期間に関しては依然不明なままであり，早急に解明すべき課題である．難治性血管炎症候群に対しては，リツキシマブ以外にTNF阻害薬を中心とした他の分子標的治療薬や生物学的製剤が新しい治療法として試みられており，今後これらの新規治療薬との比較検討が必要とされ，その結果が難治性Wegener肉芽腫症の治療におけるリツキシマブの位置づけを結論づけることとなる．

リツキシマブ投与による免疫能低下は感染症の発症や増悪に繋がる可能性がある．2006年12月，リツキシマブ投与に関して，厚生労働省よりB型肝炎ウイルスキャリアの劇症肝炎や肝不全による死亡に対する注意勧告がなされた．また，同時期には米国食品医薬品局よりSLE症例における進行性多巣性白質脳症の発症事例が公表され，注意勧告がなされた．C型肝炎を含めた各種感染症の発症やキャリアにおける増悪などに関して細心の注意が必要であり，リツキシマブを用いた臨床試験や治療に感染症という副作用が今後大きく影響する可能性は否定できない．

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Ⅶ. 腎・尿路系疾患

143. 急速進行性腎炎

Rapidly progressive glomerulonephritis, RPGN

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適応症

MPO-ANCA 型，PR3-ANCA 型，抗 GBM 抗体型急速進行性腎炎症候群

薬剤名	下限	←	常用量	→	上限
1)プレドニゾロン prednisolone, PSL (商品名：プレドニン Prednine) メチルプレドニゾロン methylprednisolone (商品名：ソル・メドロール Solu-medrol)			**0.6～1.0**mg/kg **500～1,000**mg		60mg
2)シクロホスファミド cyclophosphamide, CPA (商品名：エンドキサン Endoxan) ミゾリビン mizoribine, MZR (商品名：ブレディニン Bredinin)			**25～100**mg **3～5**mg/kg		
3)ジピリダモール dipyridamole (商品名：ペルサンチン Persantin) 塩酸ジラゼプ dilazep (商品名：コメリアン Comelian)	150mg 150mg		**300**mg **300**mg		
4)ヘパリン heparin (商品名：ノボヘパリン Novo-Heparin) ワルファリン・カリウム warfarin potassium (商品名：ワーファリン Warfarin)	5,000単位		**10,000**単位 **1～5**mg		25,000単位

使用法

1)プレドニゾロン：経口投与，朝1回食後あるいは朝昼分2にて食後．活動性血管炎の治療や副作用軽減を目的とし，大量静脈内投与を先行投与もしくは併用投与することがある(メチルプレドニゾロン：点滴静脈内注入，1日1回3日間)．

2)シクロホスファミド：経口投与，朝1回食後．血管炎症候群に対して保険適用外である．副作用軽減を目的とし間欠大量静脈内投与を選択することがある(点滴静脈内注入，0.5～1.0mg/m^2，月1回)．

ミゾリビン：経口投与，朝1回食前あるいは食後もしくは朝昼夕，分3にて食後．主に再発予防に用いられる．

3)経口投与，朝夕，分2にて食後あるいは朝昼夕，分3にて食後．

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4)ヘパリン：持続点滴静脈内注入．全血活性化部分トロンボプラスチン時間(APTT)で正常値の1.5～2.5倍を目標としモニタリングする．

ワルファリン・カリウム：経口投与，朝1回食後．治療域が狭く，効果に個人差が大きい．プロトロンビン時間国際標準比(PT-INR)2.0前後，あるいはトロンボテスト(TT)10～20％を目標としモニタリングする．

主作用

1)作用機序の詳細は不明確であるが，免疫抑制作用，抗炎症作用，腎生理機構への直接作用などを介する．

2)シクロホスファミド：ナイトロジェンマスタード類に属するアルキル化薬であり，DNA合成阻害作用がある．免疫系(Bリンパ球，Tリンパ球)機能抑制に働き，血管炎や腎炎の治療薬として用いられる．

ミゾリビン：プリン代謝拮抗(核酸合成阻害)作用があり，リンパ球の分裂・増殖を抑制することにより免疫系機能抑制に働く．

3)抗血小板作用(血小板凝集や血小板放出因子)を抑制する．

4)糸球体内過凝固に代表される血液凝固系亢進状態の是正に働く．具体的には，半月体形成に伴うフィブリン析出に反応する炎症細胞由来サイトカイン分泌抑制を目的とした，糸球体局所からのフィブリンの除去に働く．

副作用と対策

1)副腎皮質機能不全，感染症の悪化・誘発，糖尿病の悪化・誘発，消化性潰瘍，膵炎，骨頭無菌性壊死，痙攣，うつ状態，骨粗鬆症，ミオパチー，後嚢白内障，緑内障，血栓症，うっ血性心不全，肝機能障害，満月様顔貌，野牛肩，浮腫，低カリウム性アルカローシス，小児に発達障害，月経異常，多毛など多彩な副作用がある．

長期投与時の注意点として，手術，感染，過労などのストレスによる副腎クリーゼを起こしやすいこと，中止に伴う離脱症候群の可能性を念頭に置き診療にあたる必要がある．

2)シクロホスファミド：骨髄抑制，易感染性，出血性膀胱炎，排尿障害，消化器症状，間質性肺炎，肺線維症，心筋障害，抗利尿ホルモン不適合症候群，脱毛，悪心嘔吐，口内炎，性腺機能障害など．とくに用量規定因子として骨髄抑制と出血性膀胱炎があげられる．

長期投与による副作用発生を避けるために総投与量は3～8gとされているが，腎炎の治療では総投与量3g程度に抑えるほうが望ましい(25mg連日投与3ヵ月間など)．

また，腎機能障害者，高齢者においては，日和見感染を惹起することも多く，使用を控える，使用量を最小量にとどめるなどの工夫が必要である．

ミゾリビン：骨髄抑制，易感染性，間質性肺炎，高血糖，急性腎不全，肝機能障害，胃腸障害，高尿酸血症，口内炎など．腎障害時には減量が必要である．ほかの免疫抑制薬と比較し，副作用の頻度は低く，免疫抑制効果も弱い．

3)狭心症の誘発，過敏症，血小板減少，出血傾向，頭痛，動悸，熱感など．頻度の高い頭痛は少量投与にて対処可能なことが多い．

4)出血傾向，皮膚壊死(ワルファリン)，肝機能障害，ショック(ヘパリン)，血小板減少(ヘパリン)など．効果に関して十分なモニタリングを行う．ワルファリンは併用薬剤との相互作用を受けやすく，抗菌薬，高脂血症治療薬，H2受容体拮抗薬，非ステロイド性消炎鎮痛薬などとの併用にて作用が増強する．食事(ビタミンK)の影響を受けやすいので注意が必要である．

禁忌

1)消化性潰瘍，憩室炎，精神病，高血圧，血栓症，電解質異常，急性心筋梗塞既往歴，腎不全，後嚢白内障，緑内障，最近の内臓手術，結核性疾患，有効な抗菌薬のない感染症，全身の真菌症，単疱疹性角膜炎など．免疫能低下のためワクチン類の併用接種は禁忌である．

2)強い骨髄抑制，重症感染症，妊婦には禁忌である．

3)過敏症の既往歴，妊婦，出血病変，出血傾向のある患者には禁忌である．

4)過敏症の既往歴，妊婦(ワルファリン)，重篤な肝障害，出血病変，出血傾向のある患者には禁忌である．

解説

本邦における急速進行性腎炎は全身性血管炎によるものが高頻度であり，腎病変のみならず他臓器病変にも注意を払い治療を行う必要がある．

厚生労働省進行性腎疾患RPGN分科会による診療指針が公表されており，MPO(ミエロペルオキシダーゼ)-ANCA(抗好中球細胞質抗体anti-