using Student's t test for nonpaired samples, and by the χ^2 test. The evolution of the clinical parameters was analyzed in both groups by repeated measures analysis of variance. When differences could be demonstrated, values were compared with the baseline using the paired-sample t test. A p value of less than 0.05 was considered to denote statistical significance. Stepwise multiple regression analysis was used to identify independent risk factors among the parameters selected by univariate analyses. The parameters with an F value of more than 4 were adopted. A p value less than 0.05 was considered to denote statistical significance. Survival was assessed by the Kaplan–Meier method. All statistical analyses were performed using the JUMP 7 software (SAS Institute, Cary, NC, USA).

Results

Clinical features and laboratory findings

Of the 73 patients, 23 were men and 50 were women, with a mean age at diagnosis of 71±10 (range, 41–90) years. The laboratoty data (Table 1) and pattern of organ involvement during the 2-year follow-up are shown in Fig. 1. At the time of diagnosis, 71 patients (97%) had renal vasculitic involvement. At the first admission, dialysis therapy was initiated in 19 patients, of whom 2 recovered and did not require further dialysis. A total of 49patients (67%) had systemic manifestations of vasculitis, such as fever, weight loss, and myalgia; 32 patients (44%) had pulmonary involvement, manifesting as abnormal findings on chest X-rays or CT images. The pulmonary involvement was most frequently represented by interstitial pneumonia (32.9%), followed in frequency by pulmonary hemorrhage (8.2%). The diagnosis of interstitial pneumonia was based on chest CT. Eleven patients (15%) had neurological involvement; 7 patients (10%) had sensory peripheral neuropathy; 5 patients (7%) had mononeuritis multiplex; 9 patients (12%) had cutaneous involvement, mostly purpura; 6 patients (8%) had cardiovascular involvement, mainly pericarditis. Serum titer of MPO-ANCA was a mean titer of 338.4±254.1 EU, and serum CRP was 7.9±7.1 mg/dL. Serum PR3-ANCA was negative (1.0±3.7 EU).

Outcome

The patient life survival rate is shown in Fig. 2. The survival rate at 6 months after the diagnosis was 84.4% and that at 2 years after the diagnosis was 79.5%. Fifteen patients (20.5%) died during the 2-year follow-up. Infection during therapy of active vasculitis, such as interstitial pneumonia and pulmonary bleeding, was the cause of seven deaths; infection alone accounted for five deaths, active vasculitis alone for two deaths, and cardiac involvement or VT for one death. The complicating infections which caused death were *Pneumocystis jiveroci* pneumonia in four patients, *Cytomegalovirus* infection in three patients, and sepsis and bacterial pneumonia in three patients. The renal survival rate at 6 months after diagnosis was 60.2% and that at 2 years after diagnosis was 57.5%.

Change of the BVAS

We assessed the changes in the BVAS during the 2-year follow-up period. The mean BVAS, which was 16.2±5.5 at the time of diagnosis (Table 1), decreased dramatically by 1 month after the diagnosis to 1.4±4.0. The BVAS decreased to 0, suggestive of remission, in 62 patients (85%). The rate of complete remission at 2 years without deceased patients was 94.7%. After falling once to 0, the BVAS increased again in 11 patients (15%), suggestive of relapse. We found no correlation between the BVAS and the

Table 1 Clinical features during 2-year follow-up period

	At diagnosis, N=73	1 month, N=72	3 months, N=63	6 months, N=60	2 years, N=54
Cre (mg/dL)	4.0±2.6	3.0±2.1	2.4±1.6	2.1±1.1	2.2±1.8
eGFR (mL/min/1.73 m^2)	16.9±16.6	22.0±17.3	22.5±17.5	25.0±16.9	25.0±16.0
Albumin (g/dL)	2.9±0.7	3.2±0.5	3.4±0.6	3.6±0.6	3.9±0.4
CRP (mg/dL)	7.9±7.1	1.1±2.6	0.8±2.0	0.4±1.0	0.6±1.4
MPO-ANCA (EU)	338.4±254.2	136.2±176.4	35.7±82.0	11.8±22.7	5.3±87.8
U-P (g/day)	1.3±1.2	1.0±1.1	0.8±1.4	0.4±0.7	0.1±0.3
U-RBC (/HPF)	54±37	32.9±37.8	11±15	6±9	3±6
BVAS (new/worse)	16.2±5.5	1.4±4.0	0.8±2.7	0.3±1.1	0.5±2.1
BVAS (persistent)	1.8±2.8	5.8±2.3	4.8±2.8	3.8±2.8	3.2±2.2

Values are expressed as mean±SD

Cre serum creatinine, *eGFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *U-P* proteinuria, *U-RBC* urinary red blood cell, *NS* not significant

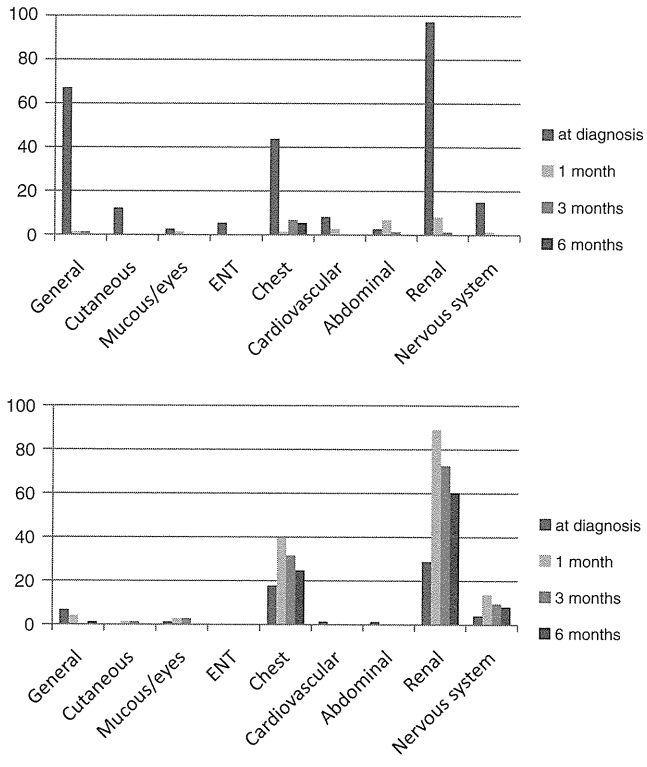

Fig. 1 Changes in the incidence of organ involvement in patients with MPA. **a** Change of the BVAS new/worse major items. **b** Change of the BVAS persistent major items. *ENT* ear, nose, and throat

serum MPO-ANCA titer, serum CRP, or UP at the time of diagnosis to the levels at 1, 3, or 6 months.

The distribution of the items of BVAS

Figure 3 shows the BVAS items in descending order of the frequency. The BVAS items of renal involvement, especially hematuria and proteinuria, were found at a high frequency. Only 20 of the 62 items of BVAS were covered in the MPA patients, excluding system involvement occurring at a frequency of 3% or lower. Thus, clustering of the BVAS items was found in the MPA patients.

Evaluation of each of the BVAS items

We analyzed the items that contributed to the total BVAS score in the MPA patients. Multiple regression analysis (Table 2) identified 10 items, including motor neuropathy ($p<0.0001$), sensory neuropathy ($p=0.0001$), pulmonary infiltrate ($p=0.0004$), hematuria ($p=0.001$), proteinuria ($p=0.003$), Cre ≥5.6 mg/dL ($p=0.01$), hypertension ($p=0.01$), scleritis ($p=0.02$), rise in Cre by ≥30% ($p=0.02$), and myalgia ($p=0.049$). Next, we analyzed the items that influenced the survival times; multiple regression analysis identified seven items, including presence of respiratory failure ($p=0.006$), congestive heart failure ($p=0.009$), Cre ≥5.6 mg/dL ($p=0.03$), organic confusion ($p=0.04$), valvular heart disease ($p=0.04$), alveolar hemorrhage ($p=0.04$), and pleurisy ($p=0.04$, Table 3).

Comparison between the high-BVAS group and low-BVAS group

We divided the patients into two groups using the median score of BVAS at diagnosis, namely the high-BVAS group and the low-BVAS group, and examined the clinical data, therapy, and the prognosis and outcome of the two groups. The comparative clinical characteristics of the two groups are shown in Table 4. There were no significant differences in the serum CRP or MPO-ANCA titers between the two groups. A significantly higher frequency of proteinuria was observed in the low-BVAS group ($p=0.015$). BVAS (persistent) score at diagnosis was higher in the low-BVAS group ($p=0.002$). There was no significant difference in the induction therapy administered between the two groups. As to the prognosis, the survival time was significantly shorter ($p=0.048$) and the mortality rate significantly higher in the high-BVAS group ($p=0.04$, Fig. 2).

Discussion

MPA has been reported to show both epidemiological and serological differences between Japan and European countries. The incidence of WG, among the ANCA-associated small-vessel vasculitides, is higher than that of MPA and/or RLV in northern Europe [13–15], whereas conversely, the incidence of MPA/RLV is markedly higher

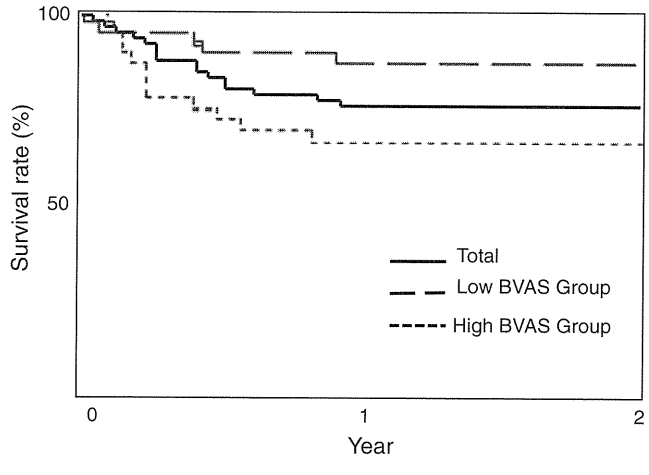

Fig. 2 Comparison of the survival rate between the high-BVAS group (≥16; $n=37$) and low-BVAS group (<16; $n=36$). *X-axis* indicates the follow-up period (in years) and the *Y-axis* the survival rate (in percent). $p=0.04$ between the high-BVAS group and low-BVAS group by the logrank test

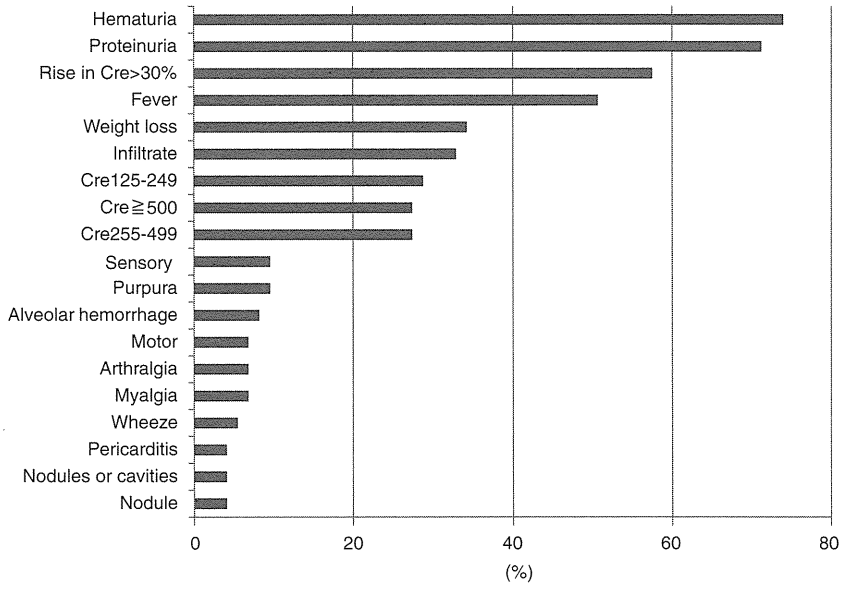

Fig. 3 BVAS items in descending order of frequency, except for items occurring at frequencies of 3% or less than

than that of WG in Japan [7]. Two nationwide Japanese surveys demonstrated that the number of patients with MPA and/or RLV is sixfold higher than that of patients with WG in Japan [7, 13–15]. In addition, serologically, MPO-ANCA-positive patients occur at a higher frequency than PR3-ANCA-positive patients in Japan, whereas patients with PR3-ANCA are more common in Europe. The percentage of patients showing seropositivity for MPO-ANCA is 79–93% in Japan, whereas it is reported to be in the range of 44–69% in Europe [7, 14]. Patients with MPA in Japan are mostly older in age than those in Europe. The mortality has also been shown to be associated with older age. The main causes of death in patients with MPA in Japan were infection and progression of vasculitis. Prophylactic therapy with trimethoprim–sulfamethoxazole was associated with a reduction in the incidence of *Pneumocystis* spp. pneumonia, with a significant decrease of the *Pneumocystis* spp. pneumonia-related mortality [16]. Because intense immunosuppression increases the risk of infections, it is necessary to use prophylactic sulfamethoxazole–trimethoprim treatment during the induction therapy and to use the minimum needed doses of the steroids or immunosuppressant drugs. In the EULARguidline, cyclophosphamide and glucocorticoids are consistently recommended as the "standard of care," but the risks of myelosuppression, infection, infertility, and malignancy with cyclophosphamide have influenced protocols aiming at minimizing cyclophosphamide exposure. MPA in Japan are mostly found in older age, especially patients 70 years old and over; dialysis-dependent people tend to avoid immunosuppressant agents. According to a nationwide survey of RPGN in Japan, immunosuppressive treatment as an initial treatment such as cyclophosphamide was administered only 21.5%. The survival rate was similar between our trial and a nationwide survey of RPGN in Japan [17].

Clinical assessment tools are important for accurate measurement of the disease activity. Serum CRP may be related to the disease activity; however, it is often difficult to distinguish between disease activity and infection based on the serum CRP. The BVAS is a validated tool for

Table 2 BVAS items which was contributed to BVAS total score (multivariate studies)

	BVAS score	*F* value	*P* value
Motor neuropathy	9	18.9	$4.73E^{-05}$
Sensory neuropathy	6	16.6	0.0001
Lungs infiltrate	4	13.7	0.0004
Hematuria ≧10 RBC/HPF	6	11.0	0.001
Proteinuria >1+	4	9.3	0.003
Creatinine ≧5.6 mg/dL	8	7.0	0.01
Hypertension	4	6.6	0.01
Scleritis	2	5.8	0.02
Rise in creatinine >30%	6	5.6	0.02
Myalgia	3	4.0	0.049

Table 3 BVAS items which was regulated to survival time (multivariate studies)

	F value	*P* value
Respiratory failure	8.2	0.006
Congestive heart failure	7.2	0.009
Creatinine ≧5.6 mg/dL	4.9	0.03
Organic confusion	4.5	0.04
Valvular heart disease	4.5	0.04
Alveolar hemorrhage	4.3	0.04
Pleurisy	4.3	0.04

Table 4 Comparison of clinical data, therapy, and prognosis between high-BVAS group and low-BVAS group

	Low-BVAS group (>16, *n*=37)	High-BVAS group (≦16, *n*=36)	*P* value
MPO-ANCA (EU)	321.5±263.6	363.3±245.2	NS
CRP (mg/dL)	6.9±6.3	9.1±7.9	NS
Alb (g/dL)	3.0±0.6	2.8±0.7	NS
Cre (mg/dL)	3.9±2.3	4.2±2.9	NS
U-protein (g/day)	1.6±1.4	1.0±0.7	0.015
U-RBC (/HPF)	61.8±38.5	44.7±34.3	NS
BVAS persistent	2.8±3.4	0.8±1.4	0.0018
Steroid pulse (*n*)	17	15	NS
PSL (mg)	35.1±14.6	32.5±19.7	NS
Cyclophosphamide (*n*)	7	11	NS
PE or DFPP (*n*)	1	3	NS
Survival time	638.9±209.3	518.9±291.8	0.048
Renal survival time	467.8±334.4	409.1±338.4	NS
Remission rate (%)	94.5	94.5	NS
Relapse rate (%)	11.1	22.2	NS
Mortality rate (%)	13.5	33.3	0.04

Survival time was significantly shorter and mortality was significantly higher in high-BVAS group than in low-BVAS group. Values are expressed as mean±SD

Cre serum creatinine, *CRP* C-reactive protein, *U-RBC* urinary red blood cell, *PE* plasma exchange, *DFPP* double filtration plasmapheresis, *NS* not significant

assessment of disease activity in systemic vasculitis [8]. The importance of BVAS is to ensure that an abnormality is recorded only when it is attributed to active vasculitis. The role of assessment of the disease activity in systemic vasculitis has been summarized as follows: (1) it assists in treatment decisions; (2) it can be used as a prognostic tool and thereby allow selection of appropriate treatment; and (3) it can be used as an outcome assessment measure (to predict morbidity and mortality). Mukhtyar et al. reported that the BVAS was correlated with the treatment decision in systemic vasculitis, but MPA patients were included in less than 10% [11]. In our study, there was no difference in the frequency of use of induction therapies, such as cyclophosphamide and steroid pulse therapy, between the high-BVAS group and low-BVAS group. One of the reasons could be that the physicians selected the therapies taking into consideration the patient's high age and the high frequency of renal dysfunction. The BVAS has also been shown to have prognostic value, at least in relation to the short- to medium-term mortality. The relationship between the initial disease activity and the risk of mortality is not clear in patients with MPA. In a large prospective cohort study of 278 patients with MPA, PAN, or CSS, Martine Gayraud showed that both FFS and BVAS at the diagnosis were predictors of a poor prognosis (p=0.04 for FFS, p<0.0002 for BVAS) [18]. We showed, by a retrospective analysis, that the initial BVAS was predictive of both the mortality and survival time in patients with MPA. FFS serves as a useful prognostic index, especially in cases of PAN and CSS. Patients with higher FFS (≥2) values at onset showed a survival advantage if they were treated with cyclophosphamide in combination with a steroid as compared with a steroid alone. In this study, some BVAS items such as congestive heart failure and Cre ≥5.6 mg/dL, which were related to the survival time overlapped with the FFS items.

Definition of the disease status is an important requirement to measure the effectiveness of treatment. The BVAS form is a useful checklist for patients with active vasculitis. The EUVAS group used definitions based on the BVAS in their trial, and BVAS 0 or 1 was defined as remission. Continued monitoring of the BVAS after remission is important. In this study, BVAS increased again after remission in 15.9% of the patients during the 2-year follow-up.

We evaluated the BVAS for the first time in patients with MPA in Japan. The majority of the BVAS items (67.7%) occurred at a frequency of less than 3% in the MPA patients. According to the French vasculitis study group, clinical manifestations observed in MPA mainly included renal manifestations (78.8%), weight loss (72.9%), skin involvement, such as purpura and livedo (62.4%), mononeuritis multiplex (57.6%), gastrointestinal tract involvement (30.6%), and lung involvement (24.7%) [18]. Lane et al. reported that ENT involvement occurred at a frequency of 29% and respiratory involvement, including interstitial pneumonia, also at a frequency of 29%, whereas renal involvement was found in 92% of the patients [9]. The clinical features of the patients in our study were generally similar to those reported by Savage et al., although a smaller proportion of our patients had renal involvement as compared with that in their report [19]. BVAS has been modified from the original BVAS to BVAS (ver.3). Some new items have been added, and some items of low specificity for vasculitis have been omitted. BVAS is not disease specific. For a comparatively rare disease, such as the

vasculitis, it would be highly desirable to develop a single standard structured clinical disease activity measure, in order to allow comparisons among different studies. However, the distribution of the BVAS items in our MPA patients was biased. To evaluate the individual organ system manifestations occurring in MPA, it is possible that a BVAS form for MPA needs to be designed to measure the disease activity.

In conclusion, we conducted this study to determine the distribution of the items of the BVAS in patients with MPA and also the changes of the BVAS during a 24-month follow-up period in patients with MPA. BVAS, which is a complex scale, but also quite detailed with multiple items, allowed estimation of the patient prognosis and of the disease activity. The individual contributions of the BVAS items may also be applied in treatment decisions.

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Disclosures None.

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ORIGINAL ARTICLE

ANCA-associated systemic vasculitis in Japan: clinical features and prognostic changes

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Abstract
Background This study was conducted to standardize treatment and determine patient and renal outcome in Japanese anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis/rapidly progressive glomerulonephritis (AAV/RPGN) patients, because the prognosis of AAV/RPGN patients in Japan had been poor compared with that of other countries.
Methods The participants in this retrospective cohort study were 824 ANCA-positive RPGN patients, 705 of whom were only myeloperoxidase (MPO)-ANCA positive.
Results Among the early-years cohort (group A; cases diagnosed between 1988 and 1998), patients frequently died due to opportunistic infection. Therefore, we recommended a reduced dose of prednisolone (oral prednisolone dose <0.8 mg/kg/day) with or without cyclophosphamide for initial treatment of Japanese RPGN patients. After this recommendation, 1-year survival of the patients improved: 75% in group A, 79% in group B (between 1999 and 2002), and 81% in group C (after 2003). During the entire observation period, average serum creatinine level at the start of treatment decreased, and improvement of 1-year renal survival was also found (72% in group A, 83% in group B, and 83% in group C), while the recurrence rate was significantly increased in group C (0.05/patient-year in group A, 0.07/patient-year in group B, and 0.13/patient-year in group C).
Conclusions Oral prednisolone dose <0.8 mg/kg/day with or without cyclophosphamide as an initial treatment could improve patient survival in older Japanese AAV/RPGN patients. However, maintenance treatment avoiding relapse should be established to improve renal outcomes.

Keywords Anti-neutrophil cytoplasmic auto-antibody (ANCA) · Immunosuppression · Prognosis changes · Rapidly progressive glomerulonephritis (RPGN) · Vasculitis

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Introduction

Recently, the wider availability of anti-neutrophil cytoplasmic auto-antibody (ANCA) assays, improved recognition of ANCA-associated vasculitis (AAV), and evidence-based treatment for AAV have resulted in longer life expectancy and avoidance of renal replacement therapy (RRT) in patients with AAV. ANCAs have been detected in patients with pauci-immune crescentic glomerulonephritis, microscopic polyangitis (MPA), granulomatosis with polyangitis (Wegener's) (GPA), and other systemic vasculitis syndromes [1, 2]. There are two major subclasses of ANCA: perinuclear (p-)ANCA and cytoplasmic (c-)ANCA [1]. The main epitope of p-ANCA is myeloperoxidase

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(MPO), and that of c-ANCA is proteinase-3 (PR3) [2]. MPO-ANCA is regarded as a useful serum marker for MPA and idiopathic pauci-immune crescentic glomerulonephritis (renal limited form of MPA), and PR3-ANCA is regarded as a serum marker for GPA and MPA [2, 3]. Furthermore, enzyme-linked immunosorbent assay (ELISA)-based serum examination for MPO-ANCA, PR3-ANCA, and anti-glomerular basement membrane (a-GBM) antibody titer tests were available in clinical settings. Several reports have suggested that, compared with PR3-ANCA-positive patients, MPO-ANCA-positive patients were older and showed predominantly chronic sclerotic lesions on histologic analysis [4, 5].

To improve the outcome of rapidly progressive glomerulonephritis (RPGN) patients in Japan, we conducted a nationwide survey of RPGN including AAV from 1998, by sending a questionnaire to 351 nephrology departments. From this survey, we concluded that 64.7% of Japanese RPGN patients had ANCAs, and among ANCA-positive patients, approximately 90% had MPO-ANCA [6].

In this study, we report the changes in treatment and outcome of Japanese AAV/RPGN patients during the last 20 years. Furthermore, we discuss the differences in clinical characteristics of ANCA subgroups in our AAV/RPGN patients.

Subjects and methods

Subjects

We retrospectively collected records of patients with RPGN from 1989 to 1998 and prospectively collected the clinical records of RPGN patients from 1999 to 2007 by sending a questionnaire annually by post to 351 nephrology departments of tertiary hospitals in Japan. This study was approved by the medical ethics committee at the Graduate School of Comprehensive Human Sciences, University of Tsukuba, in accordance with the guidelines for epidemiological research by the Ministry of Health, Labor, and Welfare of Japan. The definition of RPGN was based on clinical findings of rapidly progressing renal failure over several weeks to a few months, accompanied by the following nephritic urinary abnormalities: hematuria (mostly microscopic hematuria, but occasionally gross hematuria), proteinuria, and red blood cell cast or granular cast in urine sediment. In total, 171 nephrology departments responded and presented 1772 RPGN cases for this study. During the study period, the Japanese government decided that the PR3-ANCA test was covered by medical insurance in 1993, the MPO-ANCA test in 1998, and the a-GBM antibody test in 1999 for diagnosis of RPGN and vasculitis. Among the RPGN patients, although 1203 patients (67.9%) had ANCA [6], 824 patients received all three serological tests and presented outcome data. To analyze the effect of ANCA subclasses on patient outcomes, we selected these 824 patients for further analysis.

We evaluated AAV cases by stratifying patients into three periods depending on the year of diagnosis of AAV as previously described. Briefly, patients who were diagnosed between 1989 and 1998 were classified as group A, and data were collected retrospectively. Patients diagnosed between 1999 and 2001 were classified as group B, when we had started the analysis of Japanese cases of RPGN and part of the results had been announced in Japan during this period. Patients diagnosed between 2002 and 2007, after we had published the Japanese guideline for RPGN in 2002 [6, 7], were classified as group C.

Clinical evaluation and treatment methods

Baseline characteristics including age, sex, comorbid conditions, features of prodromal illness, and clinical, biochemical, serological, and urinary features at presentation were obtained from clinical records. Follow-up clinical data including serum creatinine level, ANCA subclasses, C-reactive protein (CRP), recurrence and survival outcome, dialysis dependence (after 1, 2, 3, 6, 12, and 24 months), start date of dialysis therapy, final follow-up date, and cause of death were also recorded. Relapse was defined as an increase in creatinine concentration with nephritic sediment and other signs or symptoms of vasculitis. The initial dose of oral prednisolone, the duration of the initial dose, and immunosuppressive treatment were also recorded.

Statistical analysis

Unpaired Student's t test was used, after a symmetrical distribution was confirmed, to determine differences in the continuous variables between groups. Otherwise, the Mann–Whitney U test was used. We used the chi-square test to analyze the frequencies of categorical variables. Both renal and patient survival rates were estimated by the Kaplan–Meier method. Prognostic factors were determined by the chi-square test, and then hazard ratios of patient outcome were estimated by the Cox regression model after confirming the proportionality in each model. To evaluate prognostic factors among the subjects at the start of treatment, we selected age, renal function (serum creatinine, urinary volume), glomerular damage (hematuria, proteinuria, cast formation), general status (serum albumin, serum total protein, hemoglobin), systemic inflammation (CRP, erythrocyte sedimentation rate, white blood cell count), and extrarenal complications (blood pressure, presence of lung involvement). Lung involvement indicates the existence of

chest X-ray abnormality, interstitial pneumonitis, or lung bleeding. We used two sets of models for analysis. The first set included age, gender, serum creatinine level at start of treatment, CRP, presence of lung involvement, and ANCA subclass. For the second set, we added initial dosage of prednisolone and cyclophosphamide usage in addition to the above variables. A p value <0.05 was considered significant. Parts of the statistical analyses were performed using SPSS software 17.0.

Results

Differences among ANCA subclasses

The study participants were 824 ANCA-positive patients, and 94.6% of the subjects had MPO-ANCA. During the last 20 years, 705 AAV patients were only MPO-ANCA positive, 34 patients were only PR3-ANCA positive, 37 patients were both MPO- and PR3-ANCA positive, 44 patients had both MPO-ANCA and a-GBM antibody, and four patients had both PR3-ANCA and a-GBM antibody. Table 1 presents the number of patients, their age, and the male-to-female ratio. Patients with only PR3-ANCA were significantly younger than those with only MPO-ANCA, and both ANCAs and a-GBM. Patients with PR3-ANCA only were predominantly male; however, patients with both ANCAs and a-GBM were predominantly female.

Table 1 Patient profile and ANCA type

ANCA type	n	Mean age (years)[a,b]	Male[a,b,c] (%)
MPO-ANCA only	705	64.4	42.6
PR3-ANCA only	34	53.6	70.6
Both ANCA	37	61.5	54.1
ANCA + a-GBM	48	65.3	29.2

[a] Statistically significant between MPO-ANCA only and PR3-ANCA only

[b] Statistically significant between PR3-ANCA only and ANCA + a-GBM

[c] Statistically significant between both-ANCA only and ANCA + a-GBM

Patients with PR3-ANCA had significantly more affected organs than both patients with MPO-ANCA and patients with both ANCAs. In particular, 65.7% of PR3-ANCA patients had ear, nose, and throat lesions, 34.3% had gut lesions, and 34.3% had skin lesions, and these involvement rates were significantly higher than in patients with MPO-ANCA. Serum creatinine levels at presentation were significantly higher in patients with both ANCAs and a-GBM antibody than for other patients (MPO-ANCA only 4.67 ± 2.84 mg/dl, PR3-ANCA only 4.51 ± 2.74 mg/dl, both ANCAs 5.08 ± 2.96 mg/dl, both ANCAs and a-GBM antibody 6.96 ± 4.08 mg/dl). CRP concentration at presentation was significantly higher in patients with PR3-ANCA only than in those with MPO-ANCA only (MPO-ANCA only 6.30 ± 6.56 mg/dl, PR3-ANCA only 9.11 ± 7.69 mg/dl, both ANCAs 6.65 ± 8.70 mg/dl, both ANCAs and a-GBM antibody 8.30 ± 8.52 mg/dl). Crescent formation rate was calculated from renal biopsy samples; patients with both ANCA and a-GBM antibody had a significantly higher crescent formation rate than patients with other types of AAV (MPO-ANCA only 57.9 ± 32.6%, PR3-ANCA only 54.4 ± 29.8%, both ANCAs 57.7 ± 28.7%, both ANCAs and a-GBM antibody 77.6 ± 22.3%).

Among the patients who were diagnosed from 1989 to 1998 (group A), from 1999 to 2002 (group B), or after 2003 (group C), ANCA subclass patterns and the proportion of patients with lung involvement were similar. The average age of the patients in both groups B and C was significantly higher than that of group A patients, and the serum creatinine level of group C patients was significantly lower than that of group A patients (Table 2).

Table 2 Patient profile by treatment period

n	ANCA subclass MPO:PR3:both:+a-GBM	Mean age (years)*#	Lung involvement (%)	Mean serum creatinine (mg/dl)#	Recurrence (n)/patient (year)#$	Initial prednisolone dose (mg/kg/day)*#$	Cyclophosphamide usage (%)
Group A							
347	284:15:27:21	60.56	50.70	5.11	0.05	0.85	41.69
Group B							
136	116:5:6:9	65.01	55.00	4.52	0.07	0.79	45.16
Group C							
341	305:14:4:18	66.88	58.80	4.19	0.13	0.71	33.67

* $p < 0.05$ between groups A and B

# $p < 0.05$ between groups A and C

$ $p < 0.05$ between groups B and C

Renal and patient survival

Cumulative patient survival rate and renal survival rate by Kaplan–Meier analysis are shown in Fig. 1. The median follow-up duration was 19.1 months (range 0–211.8 months). Cumulative patient survival rate at 12 months was 79.1%, and cumulative renal survival at 12 months was 78.4%. We further analyzed both patient survival rate and renal survival rate separated by treatment period by Kaplan–Meier analysis (Fig. 2). The median follow-up durations were 42.9, 33.2, and 10.3 months in groups A, B, and C, respectively. Patient survival rate in group C was significantly improved compared with that in group A (6-month cumulative patient survival rate: group A 77.5%, group B 81.0%, group C 85.1%; 12-month cumulative patient survival rate: group A 75.0%, group B 79.3%, group C 81.3%; $p < 0.05$). Cumulative renal survival rates in groups B and C were significantly higher than that in group A (6-month renal survival rate: group A 73.3%, group B 84.3%, group C 83.9%; 12-month renal survival rate: group A 71.7%, group B 83.3%, group C 82.8%; $p < 0.05$). Patient survival rate was slightly improved in group B compared with group C; however, renal survival was slightly exacerbated. Furthermore, the recurrence rates were 0.05, 0.07, and 0.13/patient-year in groups A, B, and C, respectively (Table 3).

Table 4 presents multivariate analysis for patient survival and renal survival. Age, lung involvement (as interstitial pneumonitis or lung bleeding), renal function, and CRP level were predictors of mortality in AAV patients. ANCA subclass did not affect patient survival. Serum creatinine level at presentation was the best predictor of renal survival; in addition, age between 60 and 69 years, and a-GBM antibody positivity among AAV patients were predictors of reduced renal survival.

Treatment methods and outcome changes

As shown in Table 4, renal function was the best predictor of renal survival; we compared renal outcome according to renal function at the start of treatment. Renal outcome in patients with serum creatinine levels <3 mg/dl showed a significant improvement in groups B and C, compared with group A. However, renal outcome in patients with serum creatinine levels of 3–6 mg/dl was similar during the entire study period. Patients with serum creatinine levels >6 mg/dl showed a tendency toward poor renal outcome in group C compared with group B (Fig. 3). Figure 4 shows the initial prednisolone dosage and cyclophosphamide usage according to both renal function and treatment period. In patients with serum creatinine levels <3 mg/dl, the initial prednisolone dosage in both groups B and C was significantly lower than that in group A. In patients with serum creatinine levels of 3–6 mg/dl, the initial prednisolone dosage in group C was significantly lower than that in group A. In patients with serum creatinine levels >6 mg/dl, the initial prednisolone dosage in group C was significantly lower than that in either group A or B. The proportion of initial cyclophosphamide usage was similar among groups A, B, and C in patients with serum creatinine levels <3 and >6 mg/dl. The proportion of initial cyclophosphamide usage in group C was significantly lower than that in group A in patients with serum creatinine levels of 3–6 mg/dl.

As shown in Table 2, the initial prednisolone dosage was significantly reduced recently (group C). We further analyzed the initial dosage of prednisolone and the proportion of cyclophosphamide usage, in addition to the above variables, by forward selection methods of

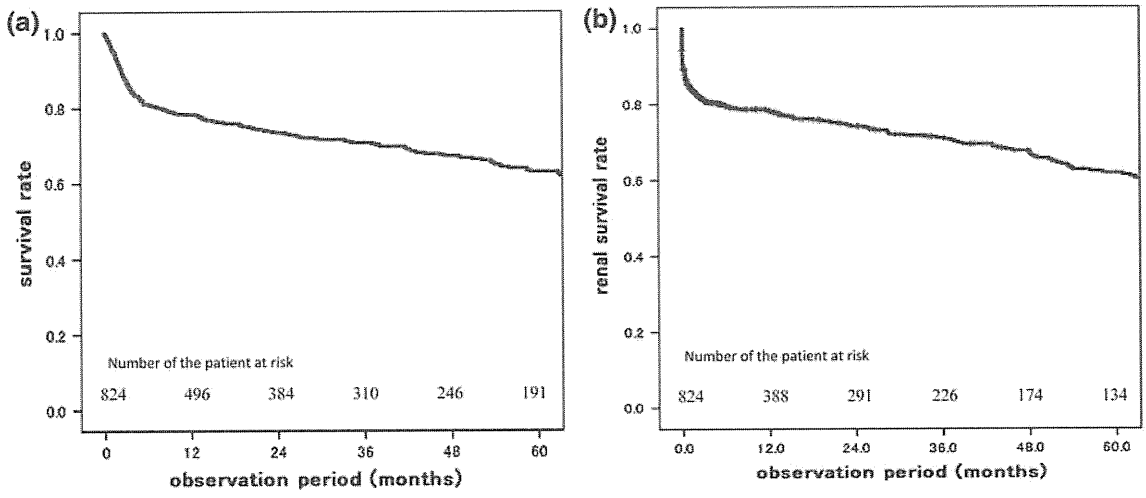

Fig. 1 Cumulative patient survival and renal survival by Kaplan–Meier analysis. **a** Patient survival: 6-month, 12-month, and 5-year cumulative patient survival rates were 81.8%, 79.1%, and 63.6%, respectively. **b** Renal survival: the 6-month, 12-month, and 5-year cumulative renal survival rates were 79.7%, 78.4%, and 62.0%, respectively

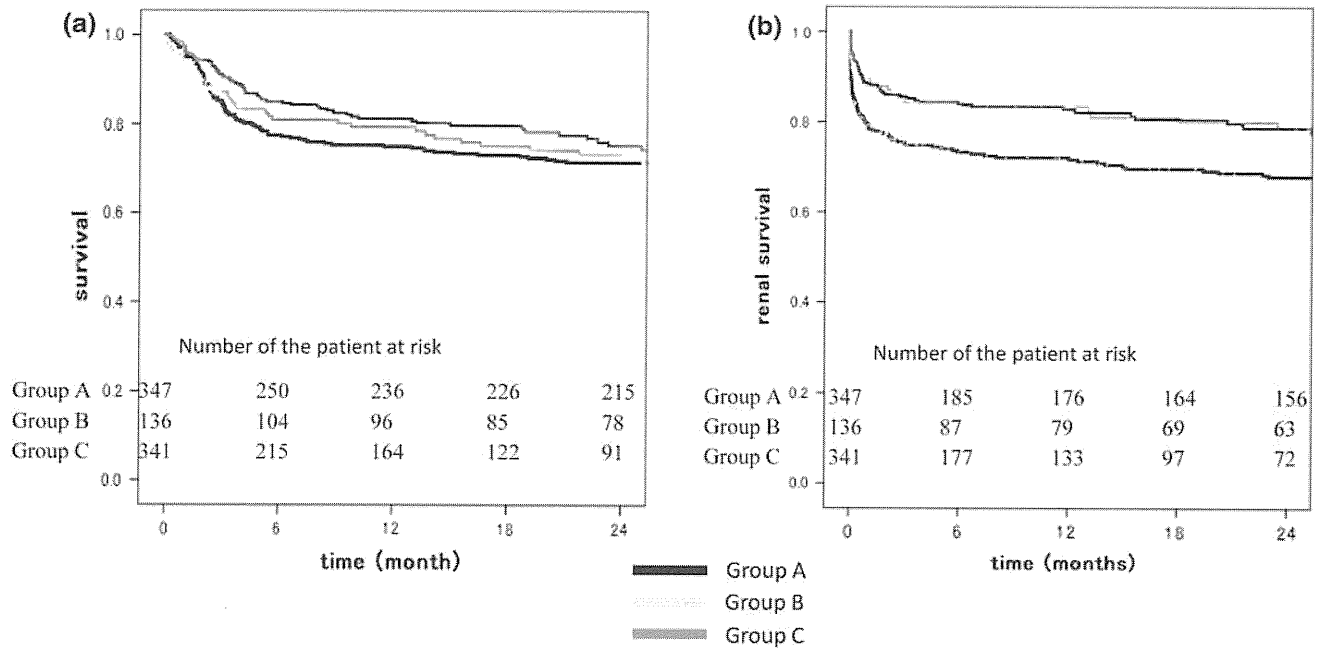

Fig. 2 Patient survival and renal survival by treatment period. **a** Patient survival: patient survival rate in group C was significantly higher than that in group A. **b** Renal survival: renal survival in groups B and C was significantly higher than that in group A. Comparing group B with group C, patient survival rate was slightly improved; however, there was no improvement in renal survival

Table 3 Multivariate Cox proportional regression analysis on predictor of death and ESRD

Factors	Death		ESRD	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (ref. <59 years)				
60–69 years	2.20 (1.54–3.16)	0.000	1.38 (0.99–1.92)	0.056
>70 years	3.32 (2.35–4.68)	0.000	1.20 (0.85–1.68)	0.301
Sex (ref. male)	1.14 (0.91–1.42)	0.265	0.92 (0.71–1.19)	0.536
Lung involvement (ref. negative)	1.94 (1.51–2.48)	0.000	0.83 (0.63–1.10)	0.199
Number of affected organs	0.98 (0.90–1.07)	0.621	0.98 (0.89–1.08)	0.725
Serum creatinine (ref. <3 mg/dl)				
3–6 mg/dl	1.85 (1.39–2.47)	0.000	3.26 (2.17–4.90)	0.000
>6 mg/dl	2.53 (1.88–3.38)	0.000	11.77 (7.96–17.40)	0.000
CRP (ref. <2.6 mg/dl)				
2.6–10 mg/dl	0.95 (0.73–1.24)	0.717	0.72 (0.53–0.98)	0.036
>10 mg/dl	1.46 (1.10–1.95)	0.010	1.22 (0.88–1.69)	0.243
ANCA subclass (ref. PR3-ANCA only)				
MPO-ANCA only	0.69 (0.42–1.14)	0.144	1.50 (0.79–2.83)	0.214
Both ANCA	0.59 (0.29–1.18)	0.135	1.72 (0.74–3.96)	0.205
ANCA + a-GBM	0.61 (0.30–1.24)	0.173	3.27 (1.50–7.11)	0.003

ESRD end-stage renal disease, *CI* confidence interval, *HR* hazard ratio

multivariate stepwise Cox proportional hazard analysis. An increase in the oral prednisolone dosage significantly reduced patient survival. The initial prednisolone dosage did not affect renal survival; however, cyclophosphamide use significantly improved renal outcome (Table 4).

Discussion

We began this survey of AAV/RPGN cases in Japan in 1998 to determine patient outcome, evaluate standard treatment patterns, and enable us to propose suitable

Table 4 Multivariate stepwise Cox proportional hazard analysis on predictor of death and ESRD (forward selection method, critical $F_{in} = 0.05/F_{out} = 0.1$)

	HR (95% CI)	*p*
Death		
Age (ref. <59 years)		
60–69 years	2.284 (1.383–3.772)	0.001
>70 years	4.286 (2.649–6.936)	0.000
CRP (ref. <2.6 mg/dl)		
2.6–10 mg/dl	0.776 (0.538–1.120)	0.176
>10 mg/dl	1.315 (0.886–1.951)	0.175
Lung involvement (ref. negative)	2.169 (1.508–3.119)	0.000
Serum creatinine (ref. <3 mg/dl)		
3–6 mg/dl	2.250 (1.474–3.434)	0.000
>6 mg/dl	2.492 (1.636–3.797)	0.000
Initial prednisolone dose (ref. <0.6 mg/kg/day)		
0.6–0.8 mg/kg/day	1.555 (0.996–2.429)	0.052
0.8–1.0 mg/kg/day	1.645 (1.005–2.692)	0.048
>1.0 mg/kg/day	2.132 (1.296–3.506)	0.003
Other variables considered: gender, ANCA subclass, cyclophosphamide usage		
ESRD		
Serum creatinine (ref. <3 mg/dl)		
3–6 mg/dl	2.811 (1.595–4.957)	0.000
>6 mg/dl	11.513 (6.827–19.416)	0.000
ANCA subclass (ref. PR3-ANCA only)		
Both ANCA	2.891 (0.788–10.611)	0.110
MPO-ANCA only	2.224 (0.699–7.077)	0.176
ANCA + a-GBM	5.403 (1.474–19.806)	0.011
Cyclophosphamide usage (ref. none)		
CYC	0.683 (0.474–0.986)	0.042

Other variables considered: age, gender, CRP, lung involvement, initial prednisolone dose

treatment guidelines for Japanese AAV/RPGN patients. During the early years of this study, we considered that the prognosis of AAV/RPGN patients in Japan was very poor compared with that of patients of different races and countries. A 1-year survival rate in AAV patients of 89% was reported in the USA [8], and 84% was reported in Europe [9], whereas the rate was 75% in our cohort during the same period (group A). We analyzed the etiology of these differences. We found that more than 90% of Japanese AAV patients had MPO-ANCA, the average age of Japanese AAV patients was high, and the most frequent cause of death was infectious complications. The standard treatment for AAV/RPGN in Europe and the USA was a combination of 1 mg/kg prednisolone and 100–200 mg cyclophosphamide [10, 11]. However, the prognosis of patients treated with high-dose prednisolone was significantly worse than that of patients treated with an oral prednisolone dose <0.8 mg/kg/day in our cohort. Furthermore, 95% of our AAV patients had MPO-ANCA (85.5% of patients were only MPO-ANCA positive), and the average age was 64.4 years. Gayraud et al. [9] reported that MPA patients above 65 years of age showed poorer outcome with use of cyclophosphamide. Based on our analysis of patients with group A and published reports, we proposed treatment guidelines for Japanese RPGN patients in 2002 [7] (Fig. 5). The guidelines emphasized the need for reduced immunosuppressive treatment, such as an initial oral prednisolone dose reduction with or without immunosuppressant, for Japanese MPO-ANCA-positive AAV/RPGN patients. With this treatment recommendation, the oral dose of prednisolone was significantly reduced and the number of patients using cyclophosphamide as an immunosuppressant was decreased.

Patient age was one of the prognostic factors for AAV/RPGN patients, and the average age of our patients was significantly increased with time; however, patient survival was significantly improved. There were several possible reasons for this. First, serum creatinine level at start of treatment was a good predictor of patient survival, and was also the strongest predictor of renal survival. Serum creatinine level at start of treatment was gradually decreased by early diagnosis and early treatment start during our observation period. Second, prophylaxis with trimethoprim/sulfamethoxazole combinations or other agents was generally used to avoid pneumocystis pneumonia in AAV/RPGN patients using immunosuppressant [12]. This prophylactic treatment was recommended in the Japanese RPGN/AAV treatment guideline [7], and was effective in reducing opportunistic infection in our most recent cohort (group C). Third, a significant reduction in prednisolone dosage and selective usage of cyclophosphamide according to treatment guideline for Japanese RPGN patients resulted in increased patient survival [6].

Although patient survival was improved with time, renal outcome of the Japanese AAV/RPGN patients was not improved. Although patients with both ANCAs and anti-GBM showed significantly poorer renal outcomes than other ANCA-positive patients, the proportion of patients with both ANCAs and anti-GBM was the same throughout our observation period. As shown in Fig. 3, renal outcome was improved by an initial serum creatinine level below 3 mg/dl; however, renal outcome was the same in the three groups in patients with serum creatinine levels of 3–6 mg/dl, and was worse in group C than in group B in those with a serum creatinine level >6 mg/dl. As shown in Fig. 5, a significant reduction in the initial prednisolone dosage resulted in a reduction in early mortality, but poorer renal outcome. de Lind van Wijngaarden et al. [13] reported a 1-year survival rate of 75% in dialysis-dependent AAV patients, and Day et al. [14] reported a rate of

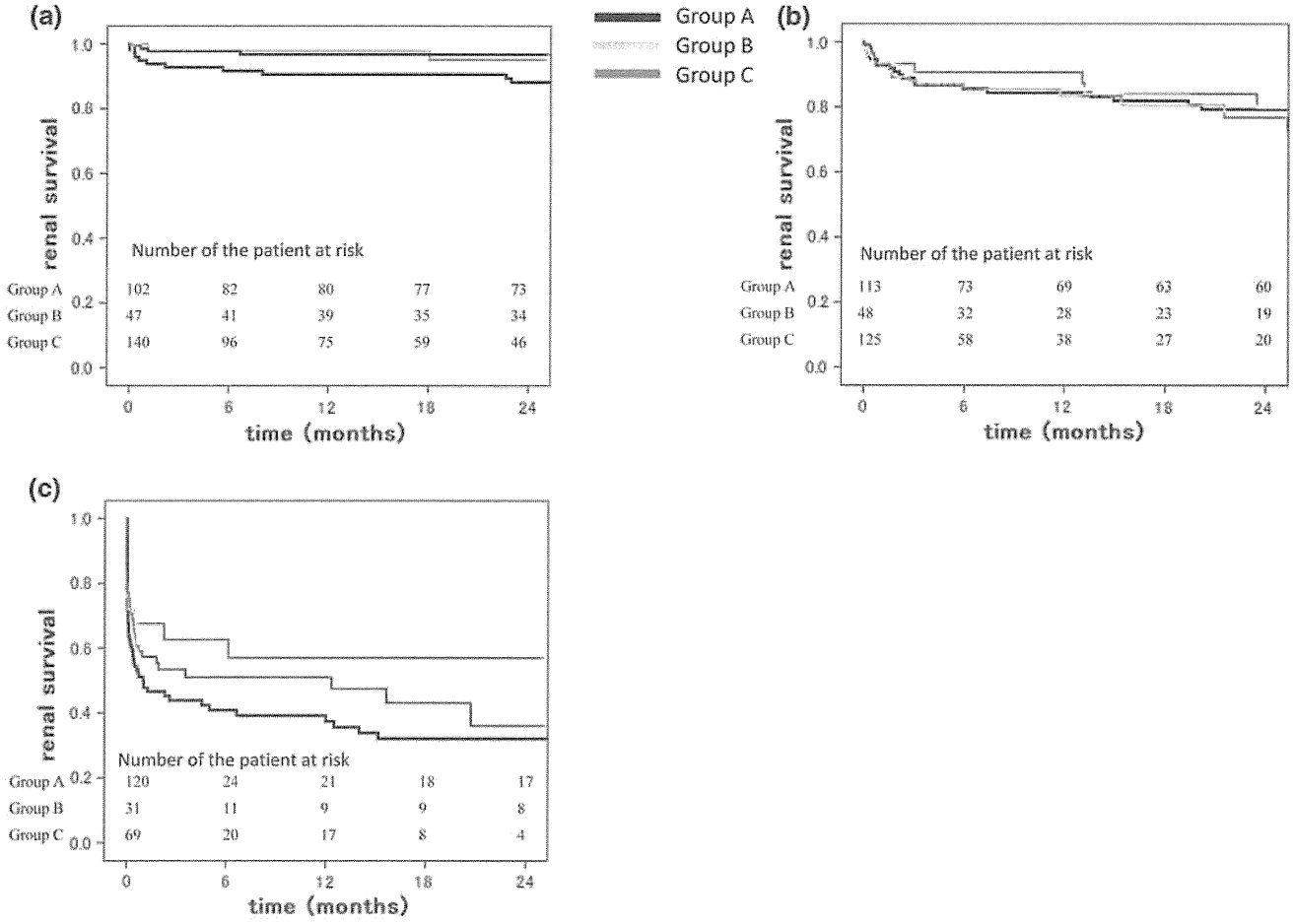

Fig. 3 Renal survival by renal function at start of treatment. Renal outcome in patients with serum creatinine levels <3 mg/dl showed a significant improvement in groups B and C, compared with group A (6-month cumulative renal survival rate: group A 91.6%, group B 97.8%, group C 97.7%; 12-month cumulative renal survival rate: group A 90.5%, group B 97.8%, group C 96.7%; $p < 0.05$). However, renal outcome in patients with serum creatinine levels of 3–6 mg/dl was not statistically different throughout the study period (6-month cumulative renal survival rate: group A 85.6%, group B 90.7%, group C 85.5%; 12-month cumulative renal survival rate: group A 84.4%, group B 90.7%, group C 83.3%; not significant). Patients with serum creatinine levels above 6 mg/dl showed a tendency toward poor renal outcome in group C compared with group B (6-month cumulative renal survival rate: group A 40.9%, group B 62.7%, group C 52.6%; 12-month cumulative renal survival rate: group A 37.4%, group B 57.0%, group C 52.6%; not significant). **a** Serum creatinine <3 mg/dl at treatment start, **b** serum creatinine 3–6 mg/dl at treatment start, **c** serum creatinine <6 mg/dl at treatment start

77% in AAV patients with an average serum creatinine level of 3.9 mg/dl, whereas in our group C patients with serum creatinine level >6 mg/dl, the 1-year survival rate was 71% and was similar in the other two cohorts. However, in our patients with serum creatinine levels >6 mg/dl in group C, the 1-year renal survival rate was 51%. Thus, renal outcome in our cohort was worse or equal to that of previously reported cohorts [13, 14, 15]. It is possible that recent patient survival improvement resulted in longer life expectancy in patients with advanced renal insufficiency, and those patients may have progressed to end-stage renal disease (ESRD). However, it is also possible that a significant reduction in prednisolone dosage in our group C patients with serum creatinine levels >6 mg/dl might result in insufficient treatment to restore their renal function.

It was reported that the recurrence rate of patients with MPO-ANCA was lower than that of patients with PR3-ANCA [3]. However, recently the selective usage of cyclophosphamide according to treatment guidelines for Japanese RPGN patients resulted in a 1.5-fold increase in the recurrence rate in Japanese AAV/RPGN patients. For treatment of active renal vasculitis, to avoid relapses, and to improve long-term renal outcomes, treatment with cyclophosphamide may be recommended; however, prolonged immunosuppression with a safer immunosuppressive agent, such as azathioprine [16], mycophenolate mofetil [17], or mizoribine [18], should be considered. We conducted a prospective randomized controlled trial with and without mizoribine for maintenance treatment of MPO-ANCA-positive RPGN (UMIN000000708). From

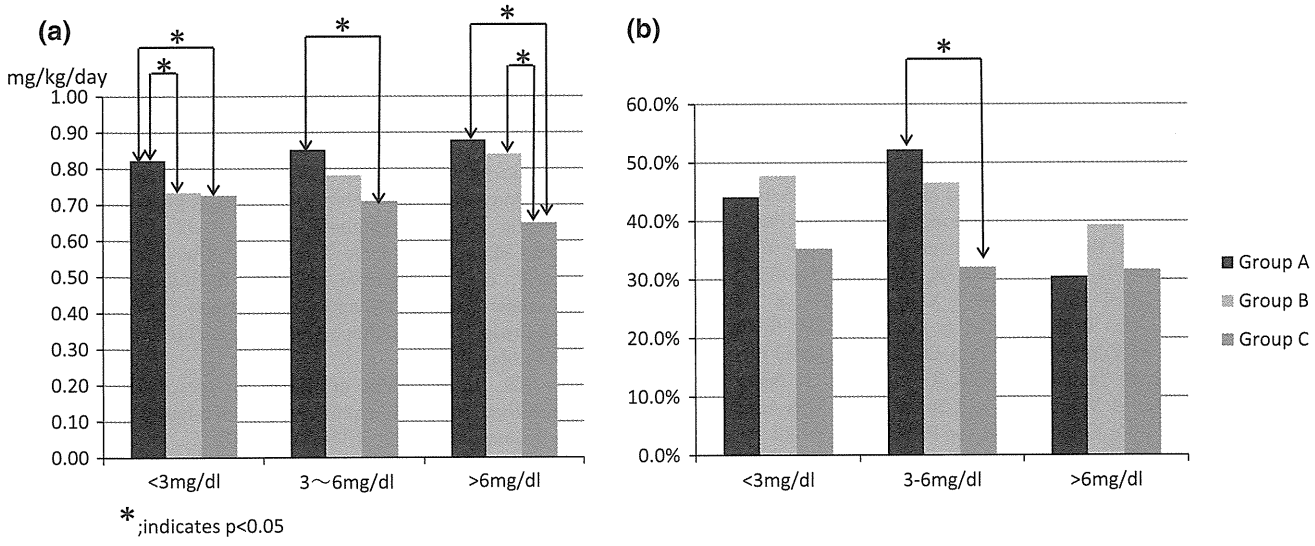

Fig. 4 Initial prednisolone dosage and cyclophosphamide usage according to both renal function and treatment period. The initial prednisolone dosage in groups B and C was significantly lower than that in group A in patients with serum creatinine levels <3 mg/dl. The initial prednisolone dosage in group C was significantly lower than that in group A in patients with serum creatinine levels of 3–6 mg/dl. The initial prednisolone dosage in group C was significantly lower than that in both groups A and B in patients with serum creatinine levels >6 mg/dl (**a**). The proportion of initial cyclophosphamide usage was not statistically different among the three groups in patients with serum creatinine levels <3 or >6 mg/dl. The proportion of initial cyclophosphamide usage in group C was significantly lower than that in group A in patients with serum creatinine levels of 3–6 mg/dl (**b**)

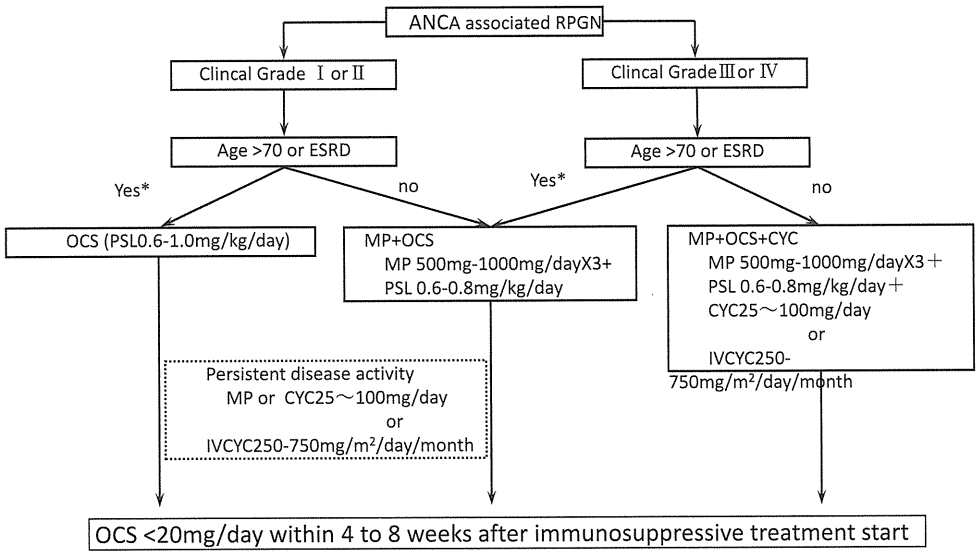

Fig. 5 Treatment algorithm for ANCA-associated RPGN in Japan. We made three treatment patterns depending on clinical grade and patient age or if the patient had already reached ESRD. The clinical grading system for RPGN was suitable for predicting patient survival. We selected age, serum creatinine level, CRP, and presence of lung involvement, because these were the strongest independent prognostic factors ($p < 0.01$) by Cox regression analysis in group A. We determined the RPGN grading system based on these four factors. All subjects were categorized into four clinical grades by the sum of the scores of the four prognostic factors [6]. After disease activity is remitted with this initial treatment method, appropriate immunosuppressant should be added for maintenance treatment

the results of this trial, we hope to identify the most suitable maintenance treatment for Japanese MPO-ANCA-positive AAV/RPGN patients.

In summary, the outcome of Japanese AAV/RPGN patients was improved after publication of the treatment guidelines in 2002 [7]; however, renal outcome of these

patients varied. To improve renal outcome, more effective maintenance treatment should be established for MPO-ANCA-positive AAV/RPGN patients.

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Conflict of interest The authors declare no conflicts of interest.

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はじめに

IgA 腎症は，臨床的には無症候性に慢性腎炎症候群として発症するが，ときに急性腎炎症候群様，あるいは稀にネフローゼ症候群の症状を呈する。したがって，腎生検された時期での臨床病理学的病期はさまざまである。IgA 腎症は腎生検により確定診断がなされるが，さらに，積極的治療の対象となる急性病変と予後を決定する慢性病変に関して，それらを総合的かつ定量的に評価することが治療方針の選択に大いに参考となる。そのため，これらの病変の多様性を病理組織学的見地から整理したのが組織分類である。厚生労働省・日本腎臓学会合同による組織学的重症度分類が 2009 年に完成し，それにより，IgA 腎症の病理組織学的スペクトラムが整理され，病変の臨床的意味が明らかにされつつある[1]。

今回の「IgA 腎症診療指針—第 3 版—　補追　IgA 腎症組織アトラス」は，豊富な図譜とその解説により，多彩な病変が理解され，IgA 腎症の組織学的重症度分類が再現性をもって使用されるように企画された。

IgA 腎症の病理総論

1．光顕像

腎疾患の病理組織分類は，1995 年に改訂された Renal disease：Classification and Atlas of Glomerular Disease (WHO)[2]を基本にしている。糸球体は，メサンギウム細胞とそれを取り巻くメサンギウム基質によって糸球体毛細血管係蹄が束ねられている。係蹄内側には内皮細胞が存在し，抗凝固作用や炎症細胞の浸潤に関与している。糸球体毛細血管係蹄の尿腔側には足細胞が位置し，さらにその外側にボウマン嚢上皮とその基底膜によってボウマン嚢腔が形成されている(**図 1**)[3]。IgA 腎症では，上記のそれぞれの構成細胞が特有の動態を示し，その結果としてメサンギウム病変，管内性病変，そして，管外性病変が形成され，それらが組み合わされて多様な糸球体病変が観察される。

IgA 腎症の病変はこのように多彩であるが，共通する病変として，傍メサンギウム領域に PAS 染色陽性，PAM 染色にて確認できる沈着物が特徴的であり，しばしば半球状沈着(hemispherical deposit)を呈する(**図 2**a, b)。IgA がメサンギウム領域に沈着し，補体の活性化を伴いメサンギウム細胞増多(mesangial hypercellularity)を引き起こす。加えて，急性病変として，管内性細胞増多(endocapillary hypercellular-

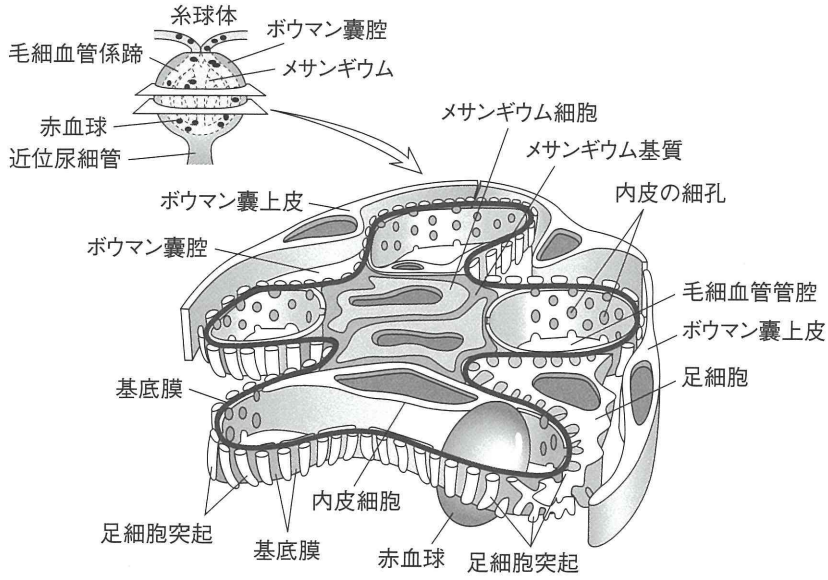

図 1　糸球体構成細胞のシェーマ
糸球体は，メサンギウム細胞とそれを取り巻くメサンギウム基質によって糸球体毛細血管係蹄が束ねられている。係蹄壁は糸球体基底膜，その内側の糸球体内皮細胞と尿腔側の糸球体上皮細胞(足細胞)により形成されている。さらにその外側にボウマン嚢上皮とその基底膜によってボウマン嚢腔が形成されている。

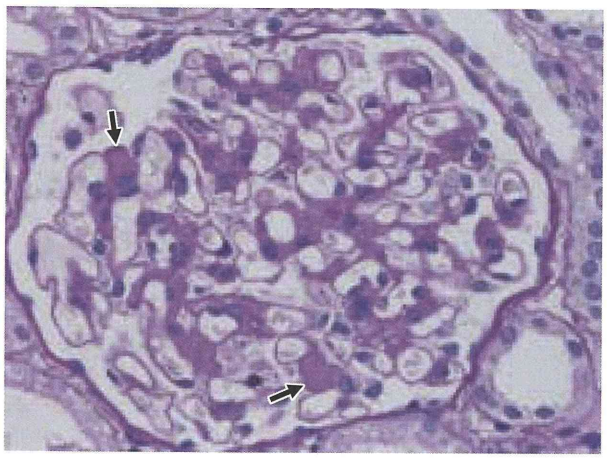

図 2a　半球状沈着物(PAS 染色)
傍メサンギウム領域に半球状沈着物を認める(矢印)。IgA 腎症の形態的特徴の一つにこの半球状沈着物(hemispherical deposit)がある。

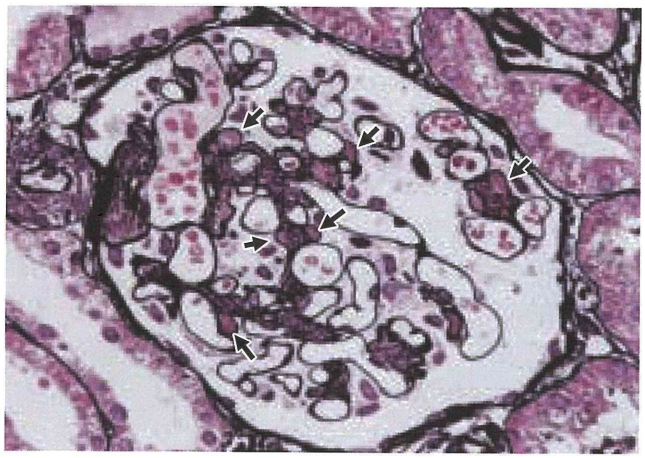

図 2b　半球状沈着物(PAM 染色)
傍メサンギウム領域の糸球体基底膜直下に多数の半球状沈着物を認める(矢印)。

ity)(糸球体毛細血管係蹄内への炎症細胞浸潤)や，糸球体毛細血管係蹄壁の壊死(tuft necrosis)，そして，活動性管外性病変(extracapillary lesion)(細胞性半月体，線維細胞性半月体)などが種々の程度に出現する。これらの病変が進行すると chronicity(慢性化)が増し，糸球体ではメサンギウム基質の増加，癒着，線維性半月体や分節性硬化を経由して，最終的に全節性硬化(球状硬化)に進展する。そして，硬化糸球体に付属する尿細管も萎縮し，腎臓内のネフロンの減少・荒廃と間質の線維化が進行する。臨床的には腎機能低下をきたし，末期腎不全へと進行する。

以上のように，IgA 腎症の組織像は急性病変から慢性病変と多彩で，しばしばそれらが混在しており，形成される糸球体病変は WHO 分類の一次性糸球体疾患で観察される糸球体病変のほとんどすべてを網羅していると言える。

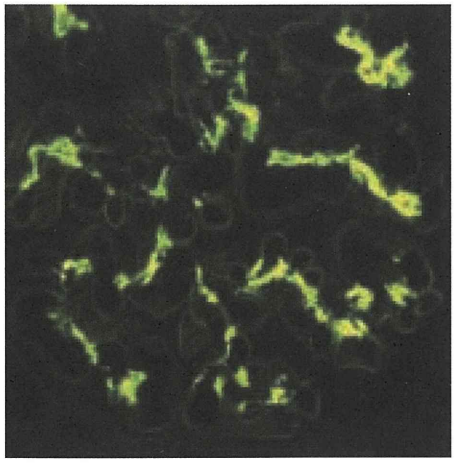

図 3　蛍光抗体法所見
（凍結切片蛍光染色　抗ヒト IgA 抗体）
IgA 腎症では，免疫染色により，糸球体のメサンギウム領域に IgA 優勢のびまん性沈着を認める。

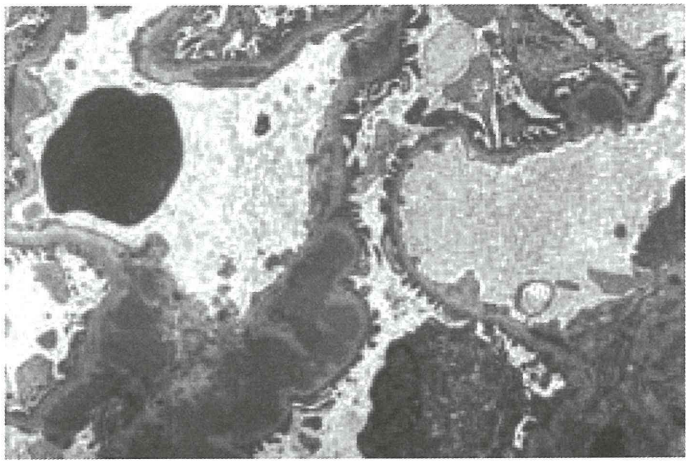

図 4　IgA 腎症の電顕像
メサンギウム領域に電子密度の高い沈着物（electron dense deposit）が確認される。

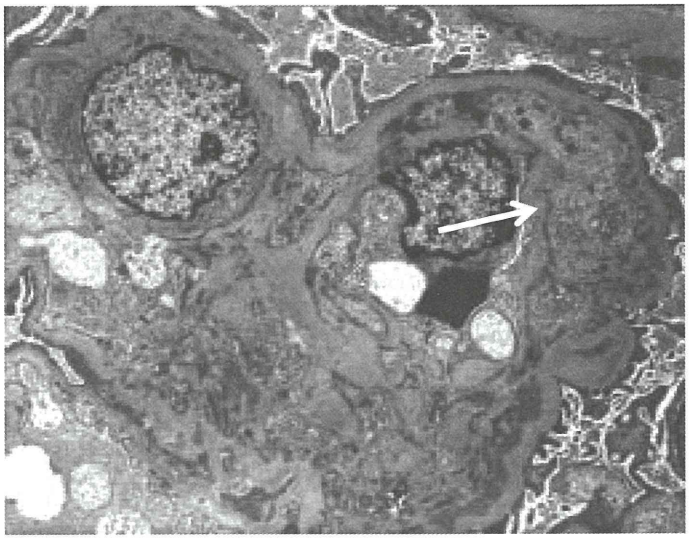

図 5　IgA 腎症電顕像（メサンギウム間入）
内皮下沈着物およびメサンギウム細胞間入（mesangial interposition）が見られる（矢印）。それにより糸球体基底膜は分裂し，PAM 染色での二重化を裏づけている。

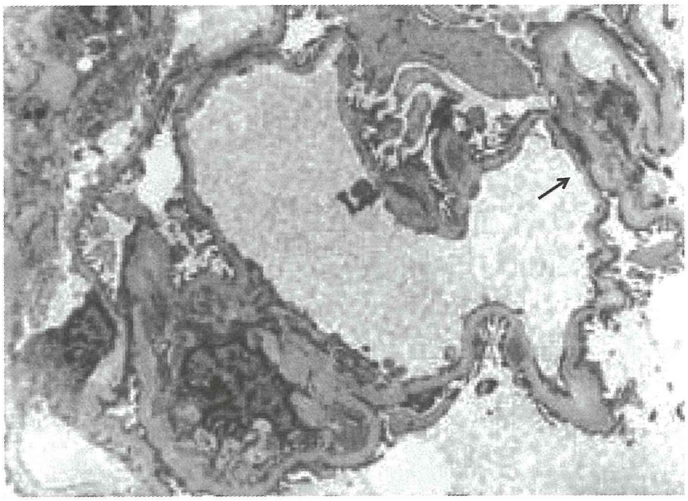

図 6　IgA 腎症電顕像（分節性の基底膜菲薄化）
糸球体毛細血管基底膜はしばしば分節性に菲薄化（矢印）する。

2．免疫染色所見

IgA 腎症は，免疫染色により，糸球体のメサンギウム領域に IgA 優勢のびまん性沈着を認める糸球体腎炎と定義される（**図 3**）。通常，C3 と IgM が IgA 沈着より劣勢に共存して沈着する。IgG の沈着は約 20〜30 %程度にみられる。C1q の沈着はきわめて稀である。

3．電顕所見

電顕像においてメサンギウム領域に電子密度の高い沈着物（electron dense deposit）が確認され IgA 腎症の診断根拠となる（**図 4**）。少量の沈着物は傍メサンギウム領域にみられることが多い。また，係蹄上皮下に不規則に上皮下沈着物を認める場合や，内皮下沈着物がみられメサンギウム細胞間入（mesangial interposition）を伴うこともある（**図 5** 矢印）。

糸球体毛細血管基底膜はしばしば分節性に菲薄化する（**図 6** 矢印）。しかし，多くの症例では，びまん性全節性に基底膜が菲薄化する菲薄基底膜病とは鑑別が可能である。

IgA 腎症の病変の定義

2009 年に国際 IgA 腎症臨床組織分類（いわゆるオックスフォード分類）として国際的なコンセンサスのもとに，上述の多彩な病変に対して詳細な定義がなされた[4]。わが国の組織学的重症度分類でも，オックスフォード分類との整合性をとり，病変の定義は原則的にオックスフォード分類のものを用いている。以下，それらについて補足を加えながら図譜をもって説明する。

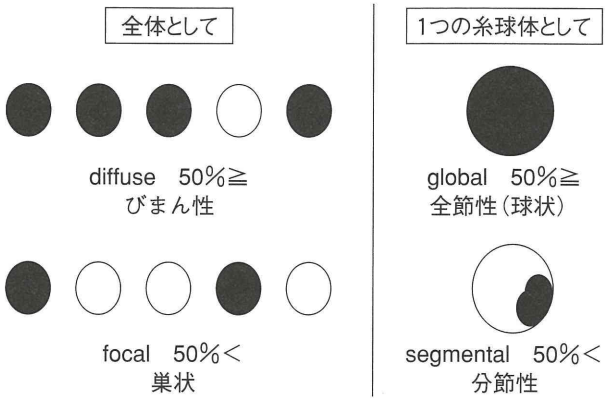

図 7　糸球体病変の拡がりの定義
オックスフォード分類やわが国の組織学的重症度分類では，糸球体病変の拡がりを 50 %で区切っている。

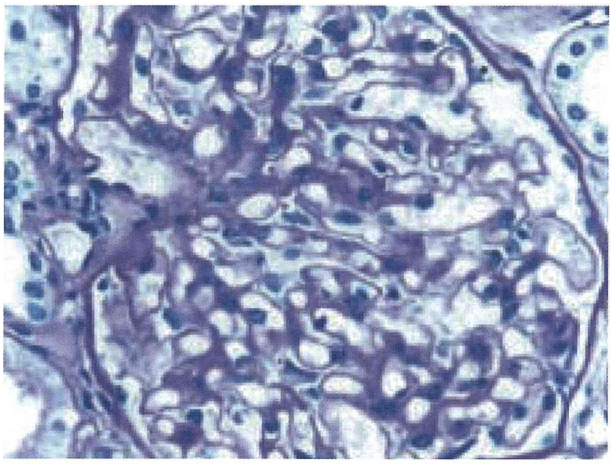

図 8a　正常糸球体（PAS 染色）
メサンギウム細胞増多における正常（normal）は，1 つのメサンギウム領域のメサンギウム細胞の核が 3 個以下と定義される。

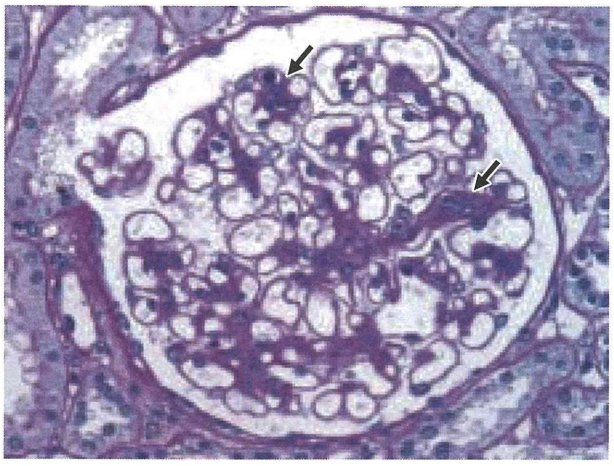

図 8b　軽度メサンギウム細胞増多
1 つのメサンギウム領域に 4〜5 個のメサンギウム細胞核が見られる（矢印）。

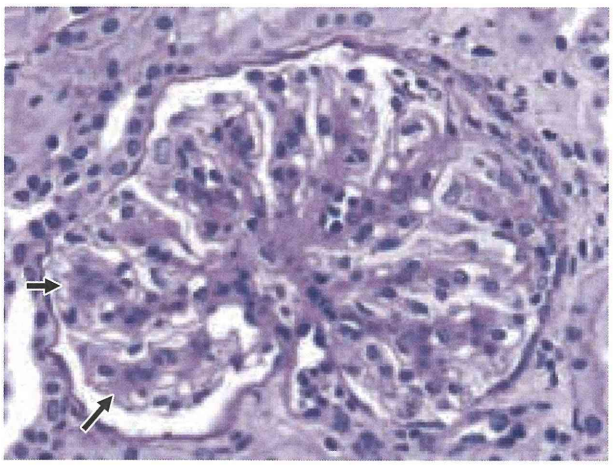

図 8c　中等度メサンギウム細胞増多
1 つのメサンギウム領域に 6〜7 個のメサンギウム細胞核が見られる（矢印）。

Ⅰ．糸球体

1．糸球体病変の拡がりの定義

病変の拡がりに関して，WHO 分類は，びまん性（diffuse）を 80 %以上，巣状（focal）を 80 %未満と定義しているが[2]，オックスフォード分類では以下のように定義されている（**図 7**）。

びまん性（diffuse）：病変を有する糸球体が採取糸球体の 50 %以上の場合

巣状（focal）：病変を有する糸球体が採取糸球体の 50 %未満の場合

全節性または球状（global）：病変が糸球体の 50 %以上に及ぶ場合

分節性（segmental）：病変が糸球体の 50 %未満の場合

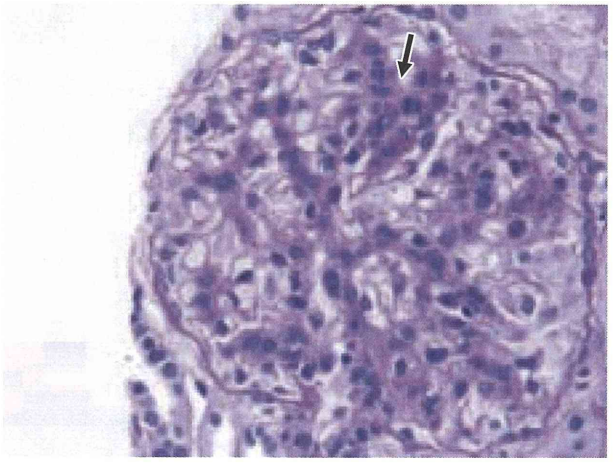

図 8d　高度メサンギウム細胞増多
1 つのメサンギウム領域に 8 個以上のメサンギウム細胞核が見られる（矢印）。

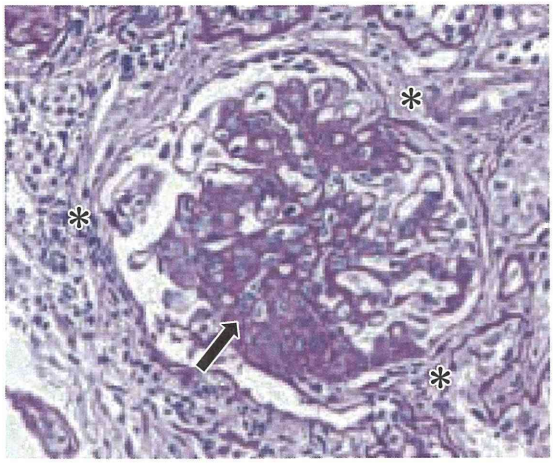

図 9a　メサンギウム基質の増加(PAS 染色)
メサンギウム細胞の核 2 個分以上の幅のメサンギウム基質が 2 カ所以上の分節に見られる。この糸球体では癒着(＊)も見られる。

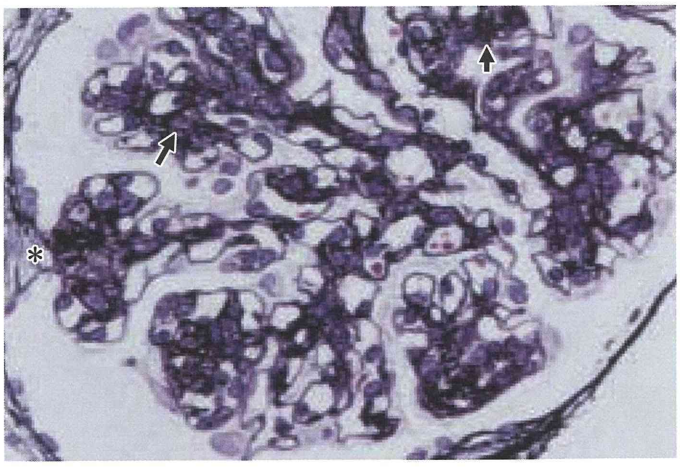

図 9b　メサンギウム基質の増加(PAM 染色)
この糸球体の矢印の部分にメサンギウム細胞の核 2 個分以上の幅のメサンギウム基質の増加が見られる。この糸球体では癒着(＊)も見られる。

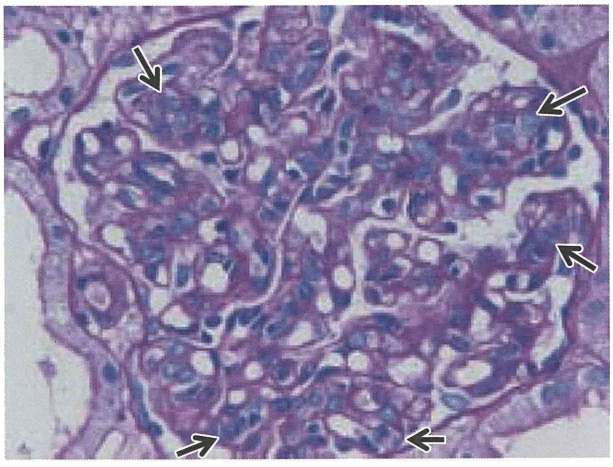

図 10a　管内性細胞増多(PAS 染色)
この糸球体では矢印で示すように広範に管内性細胞増多が見られる。管内性細胞増多とは，糸球体毛細血管係蹄内の細胞数が増加し，係蹄腔の狭小化をもたらす病変である。糸球体毛細血管係蹄内での細胞数の増加は，主としてマクロファージ浸潤であるが，内皮細胞の増殖や腫大も関与している。

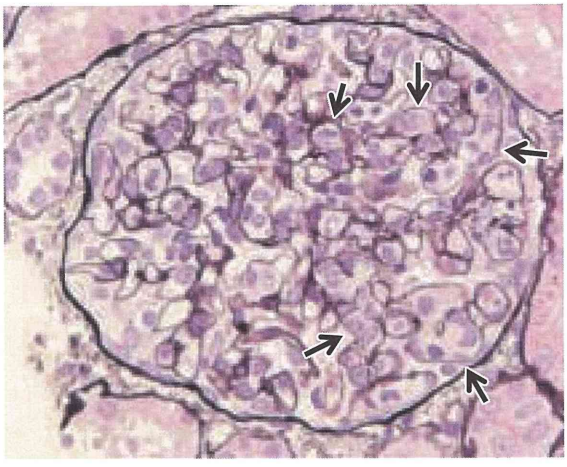

図 10b　管内性細胞増多(PAM 染色)
PAM 染色では管内性細胞増多とメサンギウム細胞増多との区別がつきやすい。この糸球体では管内性細胞増多(矢印)が主体で，メサンギウム細胞増多は目立たない。

2．糸球体における病変の定義

A．メサンギウム細胞増多(mesangial hypercellularity)

その程度に応じて以下のように分類される(国際分類では PAS 染色で 3 μm の切片で評価している)。

メサンギウム細胞増多がなく正常(normal)は，1 つのメサンギウム領域でのメサンギウム細胞が 3 個以下と定義される(**図 8a**)。

メサンギウム細胞増多の程度は，最も細胞の数の多いメサンギウム領域の細胞の数によって以下のように分類される。

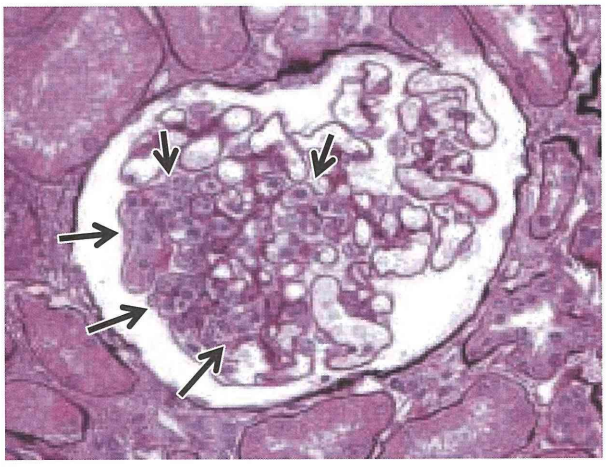

図 10c　管内性細胞増多(PAM 染色)
この糸球体では分節性に管内性細胞増多が見られる。

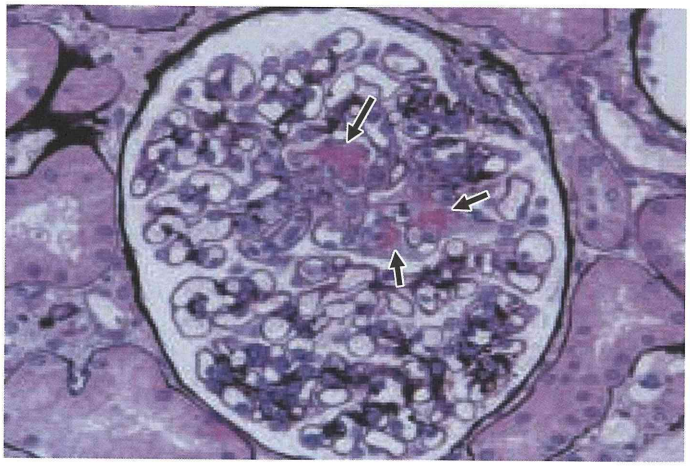

図 11　係蹄壊死(PAM 染色)
糸球体毛細血管基底膜が断裂する病変で，フィブリンの析出(矢印)を伴う。糸球体基底膜の破綻，フィブリンの析出や核崩壊の所見のうち 2 つ以上を認める場合をいう。

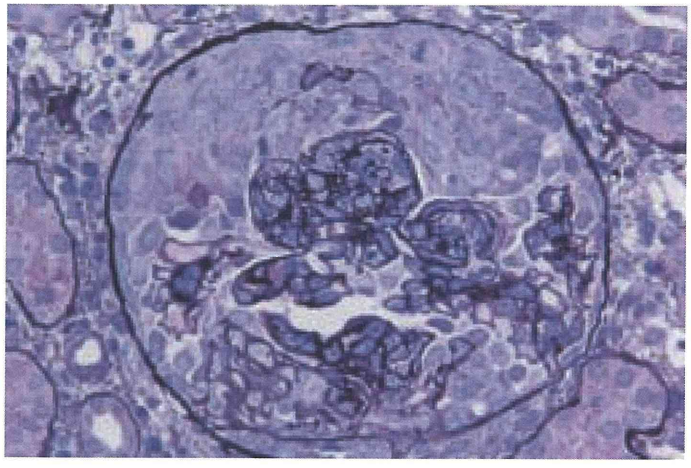

図 12a　細胞性半月体(PAM 染色)
3 層以上の管外性細胞増殖を半月体と定義し，細胞性半月体は細胞成分が 50 %以上ある半月体をいう。

軽度(mild)：1 つのメサンギウム領域に 4〜5 個のメサンギウム細胞が見られる(**図 8**b)。

中等度(moderate)：1 つのメサンギウム領域に 6〜7 個のメサンギウム細胞が見られる(**図 8**c)。

高度(severe)：1 つのメサンギウム領域に 8 個以上のメサンギウム細胞が見られる(**図 8**d)。

註) 最も細胞の多いメサンギウム領域で評価する。血管極に隣接するメサンギウム領域では評価しない。

B．メサンギウム基質増加(increased mesangial matrix)

メサンギウム細胞外基質の増加で，少なくとも 2 つのメサンギウム領域において，基質の幅がメサンギウム細胞核 2 個分を超えるものと定義される(**図 9**a：PAS 染色，**図 9**b：PAM 染色)。

C．管内性細胞増多(endocapillary hypercellularity)

糸球体毛細血管係蹄の管腔内の細胞数が増加し，管腔の狭小化をもたらす病変である。主としてマクロファージ浸潤によるものであるが，好中球浸潤がみられることがある。内皮細胞の増殖や腫大も関与している(**図 10**a：PAS 染色，**図 10**b，c：PAM 染色)。オックスフォード分類では管内領域での細胞数の増加を重視しているため，管内性細胞増多の名称を用いている。細胞増殖は本来，固有細胞が増加する意味で使用する用語である。すなわち，糸球体毛細血管係蹄内の細胞である内皮細胞の増殖に炎症細胞の浸潤が含まれて，これらの細胞を明確に判定できないことから，オックスフォード分類では管内性細胞増多と表現している[4]。

D．係蹄壊死(tuft necrosis)

糸球体毛細血管基底膜の断裂で，フィブリンの析出や核崩壊を伴う。これらの所見のうち 2 つ以上を認める場合をいう。壊死性病変は最低でもボウマン嚢腔内にフィブリンの析出を認める場合をさす(**図 11**：PAM 染色)。

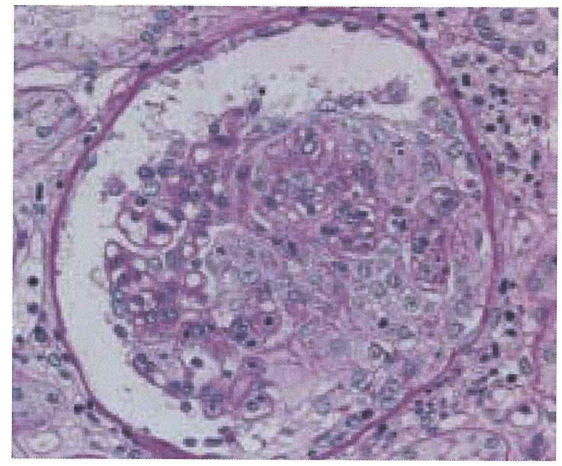

図 12b　細胞性半月体(PAS 染色)
細胞外基質増加もあるが，半月体の細胞成分が 50 %以上ある。

E．管外病変(extracapillary lesions)

以下のように分類される。

1) 管外性細胞増殖または細胞性半月体(extracapillary cellular proliferation or cellular crescent)：3 層以上の管外性細胞増殖を半月体と定義し，細胞成分が 50 %以上ある場合をいう(**図 12**a：PAM 染色，**図 12**b：PAS 染色)。病変が糸球体円周に占める%により＜10 %，10〜25 %，26〜50 %，＞50 %に分けられる。この病変はしばしばボウマン嚢の破壊を伴う。

2) 管外性線維細胞増殖または線維細胞性半月体(extra-