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SHORT COMMUNICATION

Association of HLA-DRB1*0901-DQB1*0303 haplotype with microscopic polyangiitis in Japanese

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*Microscopic polyangiitis (MPA) is a rare and severe form of systemic necrotizing vasculitis associated with myeloperoxidase (MPO)-specific antineutrophil cytoplasmic antibody (ANCA). We previously reported significant association of HLA-DRB1*0901 with MPA. To define the susceptibility loci within the HLA region, we determined the genotypes of HLA-DQB1, DPB1, B and C in 50 patients with MPA and 77 unrelated Japanese controls. In addition to HLA-DRB1*0901, significant association of DQB1*0303 (allele carrier frequencies 50% in MPA, 29.9% in controls, odds ratio 2.35, P = 0.017) was detected. These alleles were in strong linkage disequilibrium (D' = 0.95, r^2 = 0.82). Increased frequency was also observed for DPB1*0201, B*15111 and Cw*0303, which was at least partly accounted for by linkage disequilibrium with DRB1*0901 and DQB1*0303. These results indicate that DRB1*0901-DQB1*0303 haplotype represents the primary genetic risk for MPA within the HLA region in Japanese, and provides the basis that future functional studies on the role of HLA in MPA should target DR9, DQ9 and DR53 proteins encoded by this haplotype.*
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Introduction

Microscopic polyangiitis (MPA) is a rare form of systemic necrotizing vasculitis, and the patients often present with severe manifestations such as rapidly progressive glomerulonephritis, pulmonary hemorrhage and interstitial pneumonitis. MPA is strongly associated with myeloperoxidase (MPO)-specific antineutrophil cytoplasmic antibodies (ANCA). Together with other conditions associated with ANCA with specificity to MPO, proteinase 3 (PR3) or other antigens, MPA constitutes a condition collectively called ANCA-associated vasculitis (AAV).[1]

Although the etiology of AAV is poorly understood, substantial difference in the incidence among populations[2] and sporadic reports of multiplex families[3] suggest a role of genetic predisposition. With respect to MPO-ANCA associated vasculitis, previous studies reported association of HLA[4–6] and non-HLA genes,[7–10] although many of them have not been confirmed by independent studies.

In the previous study, we conducted the first multicenter study on the genetic background of AAV in Japan, and demonstrated significant association of *HLA-DRB1*0901* with MPA.[11] Since *HLA-DRB1*0901* is a common allele in Asian populations but rare in other populations, it was suggested that such a difference in the genetic background may be related to apparently higher prevalence of MPA in Japan as compared with Wegener's granulomatosis, which is more frequent in Caucasian populations.[2]

Owing to the extensive linkage disequilibrium (LD) in the HLA region, statistical association with *HLA-DRB1*0901* does not necessarily mean that *HLA-DRB1*0901* molecule is involved in the pathogenesis of MPA. In this study, we made an attempt to narrow down the region that confers susceptibility to MPA in Japanese.

Results and discussion

In view of the linkage disequilibrium structure of HLA region, allele typing was carried out for *DQB1*, *DPB1*, *B* and *C* loci on 50 patients with MPA (19 men, 31 women, mean age ± s.d. 66.1 ± 11.4 years) and 77 unrelated healthy Japanese controls (46 men, 31 women, 25.9 ± 5.6 years). Incidence of MPA in males and females appears to be approximately similar in Caucasians;[11,12] however, a nationwide study in Japan reported a female preponderance ANCA-associated vasculitis (male : female 1 : 1.8), among which MPA was most prevalent.[13] Diagnosis of MPA was based on the Japanese criteria.[14] All patients were positive for MPO-ANCA, and the diagnosis of most patients were confirmed with biopsy. The detailed explanations of the Japanese criteria and the patients' characteristics are previously described.[14] This study was

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Table 1 Alleles increased in MPA in each locus

Allele	*MPA*	*(%)*	*Controls*	*(%)*	*OR*	*95%CI*	*P*
	(n=50)		*(n=77)*				
(a) Allele carrier frequency							
*DRB1*0901*	25	(50.0)	24	(31.2)	2.21	(1.07–4.58)	0.033
*DQB1*0303*	25	(50.0)	23	(29.9)	2.35	(1.13–4.88)	0.022
*DPB1*0201*	25	(50.0)	30	(39.0)	1.57	(0.76–3.21)	0.22
*B*15111*	4	(8.0)	1	(1.3)	6.6	(0.94–46.5)	0.078
*Cw*0303*	13	(26.0)	13	(17.1)[a]	1.70	(0.72–4.04)	0.23
(b) Allele frequency							
Allele	*MPA*	*(%)*	*Controls*	*(%)*	*OR*	*95%CI*	*P*
	(2n=100)		*(2n=154)*				
*DRB1*0901*	27	(27.0)	26	(16.9)	1.82	(0.99–3.34)	0.053
*DQB1*0303*	28	(28.0)	24	(15.6)	2.11	(1.15–3.87)	0.017
*DPB1*0201*	25	(25.0)	30	(19.5)	1.38	(0.75–2.52)	0.30
*B*15111*	5	(5.0)	1	(0.7)	8.05	(1.29–50.3)	0.037
Cw*0303	16	(16.0)	15	(9.9)[a]	1.74	(0.82–3.68)	0.15

Allele typing of *HLA-DRB1, DQB1, DPB1, B* and *C* was performed by PCR-microtiter plate hybridization, PCR-preferential homoduplex formation assay or PCR-reverse sequence-specific oligonucleotide probing assays. Only the alleles that showed increase in MPA are shown. MPA = microscopic polyangiitis, OR = odds ratio, CI = confidence interval.
[a]*HLA-Cw* allele typing was unsuccessful in one control subject; therefore, total number of controls was 76 in the comparison of *HLA-Cw.*

reviewed and approved by the Research Ethics Committee of the University of Tokyo.

Table 1 lists the allele that showed an increase in MPA in each locus. *HLA-DQB1*0303* demonstrated statistically significant association as strong as *HLA-DRB1*0901. HLA-DQB1*0303* and *DRB1*0901* have been shown to be in strong LD,[15,16] which was confirmed in our control subjects ($D' = 0.95$, $r^2 = 0.82$). A tendency of increase was also observed for *HLA-DPB1*0201, B*15111* and *Cw*0303.* Among these alleles, the frequency of *B*15111* barely reached statistical significance, although the frequencies were low both in the patients and controls.

As the latter alleles have been also shown to be in LD with *HLA-DRB1*0901* in Japanese,[15,16] two-locus analysis was performed between each allele and *HLA-DRB1*0901,* to distinguish the alleles directly associated with MPA and those that reflect LD with such alleles.

As shown in Table 2A, due to the strong LD between *HLA-DRB1*0901* and *DQB1*0303,* the the numbers of the subjects carrying only one of them (group b and c) were small; thus, the effects of these alleles could not be separated. Independent contribution of *Cw*0303* was excluded (Table 2D, group c), and that of *DPB1*0201* seemed to be at best marginal (Table 2B, group c).

*HLA-B*15111* is one of the alleles coding for serological specificity of *HLA-B75.* This rare allele (one carrier in 77 controls, Table 1a) was accumulated in MPA (four carriers, one of whom was homozygous). Four of five carriers of *B*15111* including the homozygote possessed *DRB1*0901,* suggesting that *B*15111* is encoded on one of the haplotypes carrying *DRB1*0901.* Interestingly, one patient was positive for *B*15111* in the absence of *DRB1*0901* (Table 2C, group c). On the other hand, other *HLA-B* alleles in LD with *DRB1*0901* such as *B*4002* and *B*4006*[15,16] were not increased in MPA (allele carrier frequencies of *B*4002*: 14.0% in MPA, 10.4% in controls, *B*4006*: 10.0% in MPA, 11.7% in controls). These results could possibly suggest that *B*15111* itself or another gene in linkage disequilibrium with it might have a contribution independent of *DRB1*0901.*

TNF gene coding for TNFα is an obvious functional candidate. Although −308 and −238 SNPs in the promoter region of TNFα are both rare, SNPs at −1031, −863 and −857 are common in Japanese.[17] In our subjects, all haplotypes carrying *B*15111* were found to encode the major haplotype of TNFα promoter (−1031T, −863C, −857C, *TNFA-U01* haplotype).[17] This haplotype was present in 94% of MPA and 87.5% in the controls, which difference did not reach statistical significance,[14] suggesting that the increase of *HLA-B*15111* was not caused by direct association of *TNF* promoter. Thus, possible controbution of *HLA-B*15111* should be examined in the future by large-scale studies.

Our present observations indicate that *HLA-DRB1*0901-DQB1*0303* haplotype represents the major genetic risk for MPA. These alleles encode DR9 and DQ9 proteins, respectively. Owing to the strong linkage disequilibrium, it is impossible to determine which allele product is functionally relevant in the development of MPA. Furthermore, *HLA-DR9, DR4* and *DR7* alleles form the DR53 group haplotype, on which *DRB4* gene that encode DR53 protein is present. Although alleles that belong to *DR4* or *DR7* was not increased in the Japanese MPA,[14] increase of *DR4* was reported in Caucasian AAV patients,[4,5] raising the possibility that *DRB4* gene product (HLA-DR53 protein) may possibly be funtionally involved in the pathogenesis.

In conclusion, our findings demonstrated that *HLA-DRB1*0901-DQB1*0303* haplotype represents the major genetic contribution in the HLA region in Japanese. Owing to the rarity of MPA, these results should be confirmed by independent studies in the Asian populations, because of the low frequency of this haplotype in other populations. Nevertheless, our observations

Table 2 Two-locus analyses indicate primary role of *DRB1*0901-DQB1*0303* haplotype

	*DRB1*0901*	*DQB1*0303*	*MPA*	*Controls*	*OR*	*95%CI*	*P*
*(A) DRB1*0901 and DQB1*0303*							
(a)	+	+	25	22	2.36	1.13–4.95	0.023
(b)	+	–	0	2	0.41	0.02–8.90	1.0
(c)	–	+	0	1	0.69	0.03–17.4	1.0
(d)	–	–	25	52	1 (reference)		
	*DRB1*0901*	*DPB1*0201*	*MPA*	*Controls*	*OR*	*95%CI*	*P*
*(B) DRB1*0901-DPB1*0201*							
(a)	+	+	15	11	3.09	1.17–8.16	0.023
(b)	+	–	10	13	1.74	0.63–4.83	0.285
(c)	–	+	10	19	1.19	0.45–3.17	0.723
(d)	–	–	15	34	1 (reference)		
	*DRB1*0901*	*B*15111*	*MPA*	*Controls*	*OR*	*95%CI*	*P*
*(C) DRB1*0901-B*15111*							
(a)	+	+	3	1	6.63	0.86–51.2	0.19
(b)	+	–	22	23	2.11	1.00–4.48	0.05
(c)	–	+	1	0	6.55	0.26–166.6	0.32
(d)	–	–	24	53	1 (reference)		
	*DRB1*0901*	*Cw*0303*	*MPA*	*controls*	*OR*	*95%CI*	*P*
*(D) DRB1*0901-Cw*0303*							
(a)	+	+	6	5	2.11	0.60–7.49	0.32
(b)	+	–	19	19	1.76	0.79–3.92	0.17
(c)	–	+	0	8	0.10	0.006–1.85	0.048
(d)	–	–	25	44	1 (reference)		

Alleles that were increased in MPA in each locus was analyzed for the contribution independent of *DRB1*0901*. In each comparison, group d lacking both *DRB1*0901* and the allele of interest was used as a reference. When any one of the variables contained 0, OR and 95% CI were calculated by adding 0.5 to all variables.

strongly suggest that future studies on the role of HLA in the pathogenesis of MPA should target not only HLA-DR9, but also DQ9 and DR53 proteins.

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Risk Factors for Recurrent Thrombosis: Prospective Study of a Cohort of Japanese Systemic Lupus Erythematosus

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Not only antiphospholipid antibodies (aPLs) but also other factors should be considered in assessing the risk of thrombosis development in patients with systemic lupus erythematosus (SLE) and antiphospholipid antibodies (aPLs). The kinds of risk factors, including past history of thrombotic event (PHTE), hypertension, hypercholesterolemia, diabetes mellitus (DM), obesity, and smoking, in conjunction with aPLs, that contribute to the development of new thrombotic events in patients with SLE and aPLs were studied prospectively over a 5-year observation period. One-hundred and sixty-six Japanese patients with SLE (55 patients with aPLs and 111 patients without aPLs) were examined and followed up for 5 years. Five major risk factors for ischemic coronary disease and stroke according to the Framingham heart cohort study were evaluated objectively in these patients. A significant difference was seen for 4 factors: past history of thrombotic event (PHTE; odds ratio: 101.93; 95% confidence interval: 12.29–845.22; $p<0.0001$), hypertension (odds ratio: 8.87; 95% CI: 2.58–30.53; $p<0.001$), DM (odds ratio: 5.42; 95% CI: 1.44–20.46; $p<0.05$), and lupus anticoagulant (LAC; odds ratio: 47.41; 95% CI: 5.88–382.03, $p<0.0001$) as aPLs, when the incidence of these risk factors was compared between patients with and without new thrombotic events. Furthermore, PHTE (odds ratio: 30.19, 95% CI: 1.33–683.13), hypertension (odds ratio: 15.44; 95% CI: 1.77–134.80), and LAC (odds ratio: 14.11; 95% CI: 0.48–412.42) showed higher odds ratios than DM (odds ratio: 11.53; 95% CI: 0.83–159.94) on multivariate logistic analysis as well as analysis of the combination of risk factors, suggesting that these are important risk factors for the development of new thrombotic events in patients with SLE and aPLs.

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Introduction

Ever since Graham Hughes first reported antiphospholipid syndrome (APS; Hughes' syndrome),[1] which is characterized by thrombosis, thrombocytopenia, and recurrent fetal loss in patients with systemic lupus erythematosus (SLE) who are positive for antibody to negatively charged phospholipid molecules such as cardiolipin, antiphospholipid antibodies (aPLs) have been considered as a risk factor of thrombosis.[2-5] In general, the incidence of death due to throm-

bosis differs among racial and ethnic populations. Risk of death due to ischemic heart disease in Japan is less than 30% of that in the United States. However, the risk of death due to cerebral infarction in Japan is more than double the risk in the United States.[6,7] In addition, data indicate that Japanese men of similar ancestry demonstrate consistent declines in stroke incidence with increases in the distance of migration from Hawaii to California.[8] These findings suggest that changes in risk factors according to this migration play an important role in altering the risk of stroke, independent of potential genetic influences. However, the importance of racial factors in patients with APS remains unclear. To clarify these issues, we prospectively studied the kinds of risk factors including past history of thrombotic event (PHTE), hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking, and aPLs that contribute to the development of thrombosis in Japanese patients with SLE over a 5-year observation period.

Methods

Patients

One hundred and sixty-six Japanese patients with SLE were registered at Juntendo University Hospital in 1997 and followed up over a 5-year period. All patients fulfilled the 1982 American College of Rheumatology (ACR) criteria for SLE[9]; aPLs were positive in 55 and negative in 111 of the 166 patients. These patients were examined and followed up over a 5-year period from January 1, 1997, to December 31, 2001. Clinical findings were observed and laboratory examinations were carried out monthly. All patients with aPLs were treated with a low or medium dosage of prednisolone (PSL) ranging from 10 to 30 mg/day and a low dosage of aspirin (81 mg/day) and/or ticlopidine (300 mg/day).

Laboratory Examinations

Serum total cholesterol concentrations were determined by using the Clinical Analyzer 7350 (Hitachi Ltd., Tokyo, Japan) utilizing the enzyme assay method (TC-K, Keinos Co., Tokyo, Japan). Lupus anticoagulant (LAC) was detected by the modified mixing Kaolin clotting time as described previously.[10,11] Immunoglobulin G (IgG) anticardiolipin antibodies (aCLIgG) were measured by a recently developed ELISA Kit "MESA CUP Cardiolipin Test" (MBL Co., Tokyo, Japan) (normal value <1.0 U/mL), which consists of the method described by Harris et al.[12] β2glycoprotein I-dependent aCL (β2GP1-aCL) was measured by EIA Kit "Anti CL β2 GP1 Kit"[13] (Yamasa Sho-yu Co., Chiba, Japan) (normal value <1.2 U/mL).

Risk Factors

In the Framingham heart study cohort, several important risk factors for ischemic coronary disease and stroke were noted.[14,15] Five major factors: hypertension, hypercholesterolemia, diabetes mellitus (DM), obesity, and smoking were selected for evaluation in this study. These factors in patients with SLE were evaluated objectively. Furthermore, PHTE was added as 1 of the risk factors because PHTE is thought to be an important risk factor for future thrombotic events in patients with APS. Thus, we investigated whether hypertension, hypercholesterolemia, DM, obesity, smoking and PHTE contributed to thrombotic events in patients with SLE and APS. The above-listed risk factors were examined in all patients in this series. Hypertension was diagnosed by use of the 1993 WHO/ISH classification criteria.[16] Fasting total cholesterol levels were measured and serum total cholesterol concentrations greater than 220 mg/dL were defined as hypercholesterolemia. DM was diagnosed by use of the 1997 American Diabetes Association (ADA) criteria for diabetes and hyperglycemia.[17] Obesity was determined by the 1995 Japanese criteria for body weight and obesity (Japanese Society of Obesity and the Japanese Ministry of Health, Labor and Welfare[18]). These criteria described individuals with body mass index (BMI) greater than 25 as overweight and those with a BMI greater than 30 as obese. It was noted that glucose tolerance insufficiency was found in the overweight Japanese population.[19] Thus, these overweight populations were included in the obesity group. Treatment for these risk factors varied from patient to patient.

Statistical Analysis

Data entry and analysis were performed with the SPSS statistical software package (SPSS Inc., Chicago, USA). Correlation of thrombotic events and thrombotic risk factors was analyzed by use of two-by-two contingency tables, and p values were estimated with the Fisher's exact test. Binary

logistic regression analysis was used for the evaluation of risk factors in the development of thrombosis during the study period.

Results

Study Patients Profile

There was no significant difference in the incidence of hypertension, hypercholesterolemia, obesity, and DM between patients with and without aPLs. The incidence of smoking in patients without aPLs was significantly greater than that in those with aPLs. The number of patients with PHTE in the patients with aPLs (45.5%) was significantly greater than that in those without aPLs (0.9%) (Table I).

Incidence of Thrombotic Events

During the 5-year study period, 12 patients developed various thrombotic events. As shown in Table II, 5 patients had cerebral infarction and 2 had myocardial infarction. Pulmonary artery thromboembolism, skin ulcer, external shunt failure, miscarriage with thrombosis of the placenta, and valvular thrombus formation also developed in 1 patient each. Of the risk factors, 11 patients (91.7%) had PHTE, 7 had hypertension (58.3%), 4 each had hypercholesterolemia and DM (33.3%), and 1 patient had smoking. All patients demonstrated aPLs, and LAC was positive in 11 of 12 patients.

Correlation Between Development of Thrombosis and Risk Factors

We estimated the unadjusted odds ratio of each thrombotic risk factor and aPLs test for new development of thrombotic events during the study period (Table III). Significant differences could be seen for 4 risk factors. These were PHTE (odds ratio: 101.93; 95% CI: 12.29–845.22; $p < 0.0001$), hypertension (odds ratio: 8.87; 95% CI: 2.58–30.53; $p < 0.001$), DM (odds ratio: 5.42; 95% CI: 1.44–20.46; $p < 0.05$), and LAC (odds ratio: 47.41; 95% CI: 5.88–382.03, $p < 0.0001$) (Table III). The odds ratio for obesity, smoking, and hypercholesterolemia were low, and there were no significant differences in incidence of new thrombosis between patients with and without each risk on chi-square test.

Concerning aPLs, aCLIgG and β2GPI-aCL had low odds ratio, and there were also no significant differences in the frequencies of new thrombotic events between the patients with and without these antibodies. We also estimated the unadjusted odds ratio for a combination of 3 aPLs. However, there were no statistically meaningful correlations; aCLIgG tended to increase the incidence of thrombosis by combination with β2GPI-aCL and/or LAC, but, such a tendency was not recognized in LAC.

Evaluation According to Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis was performed to estimate the adjusted effects of risk factors on new thrombotic events during the study period. We estimated the adjusted odds ratio for comparison of findings. We adopted 4 predictive variables that had statistically significant high odds ratios from the risk factors tested in multivariate regression formula. These were PHTE, hypertension, DM, and LAC. PHTE showed the highest odds ratio (30.19, 95% CI: 1.33–683.13), followed by hypertension (odds ratio: 15.44; 95% CI: 1.77–134.80), and LAC (odds ratio: 14.11; 95% CI: 0.48–412.42). DM (odds ratio: 11.53; 95% CI: 0.83–159.94) had the lowest odds ratio (Table IV).

Odds Ratio Combination of 2 Combined Risk Factors

Odds ratios for combinations of the 4 risk factors were compared. As shown in Table V, combination of 2 risk factors (hypertension and PHTE, 76.0; hypertension and LAC, 76.0; LAC and PHTE, 54.2) had higher odds ratio than any single risk factor.

Discussion

Antibodies called aPL have been thought to be a cause of venous and/or arterial thrombosis in patients with SLE. However, patients with SLE and aPLs frequently have other risk factors for thrombosis (eg, DM, hypertension, hypercholesterolemia, obesity). Therefore, prospective studies are necessary to evaluate the role of aPLs as a risk factor for thrombosis and eventually include it on the list of other known cardiovascular and cerebrovascular risk factors. In addition, it has been re-

Table I. Patient profile of antiphospholipid antibody-positive group and antibody-negative group.

	Antiphospholipid Antibodies		
	Positive	Negative	p Value
Number of patients	55	111	
Age, mean ± SD, years	40.6 ±12.9	42.6 ± 13.9	0.378
Gender, male/female	3/52	10/101	0.548
Risk factors case, n (%)			
PHTE	25 (45.5%)	1 (0.9%)	<0.001
Hypertension	10 (18.2%)	18 (16.2%)	0.826
Hypercholesterolemia	10 (18.2%)	32 (28.8%)	0.184
Obesity (BMI ≥ 25)	3 (5.5%)	8 (7.2%)	1.000
Smoking	1 (1.8%)	27 (24.3%)	<0.001
Diabetes mellitus	4 (7.3%)	13 (11.7%)	0.430
Antiphospholipid antibodies			
aCLIgG	20 (36.4%)	0 (0.0%)	<0.001
β2GP1-aCL	21 (38.2%)	0 (0.0%)	<0.001
LAC	40 (72.7%)	0 (0.0%)	<0.001
Antithrombotic therapy			
Low-dose aspirin	54 (98.2%)	0 (0.0%)	<0.001
Oral anticoagulant	2 (3.6%)	1 (0.9%)	<0.001
Antihyperlipidemia therapy			
Statin	7 (12.7%)	29 (26.1%)	0.135
Nonstatin	3 (5.5%)	3 (2.7%)	0.135

PHTE: past history of thrombotic events; aCLIgG: IgG anticardiolipin antibody; β2GP1-aCL: β2GPI dependent anticardiolipin antibody; LAC: lupus anticoagulant; NS: not significant.

ported that young patients with SLE tend to have arteriosclerosis.[20] It has also been reported that there is a 50-fold increase in the incidence of ischemic cardiovascular events among female patients with SLE between 35 and 44 years of age compared to that in age-matched healthy female subjects,[21] and an increased risk for the development of cerebral infarction could also be seen.[22,23] In this paper, risk factors including the known cardiovascular and cerebrovascular risk factors, and aPLs, for development of new thrombotic events in patients with SLE and APS were studied prospectively over a 5-year observation period.

The incidence of APS in patients with SLE is very high, ranging from 20% to 30%.[24,25] In this cohort study, patients with SLE but without aPLs had no thrombosis for 5 years. All of the 12 thromboses occurred in patients with aPLs. Thus,

Table II. Profiles of female patients with new thrombosis in study period.

No.	Age	Lesion	Risk Factors	Laboratory Findings			Treatment		
				LAC	aCLIgG	β2GPI-aCL	Anti-hypertensive	Anti-hyperlipidemia	Glucocorticoid
1	53	Skin ulcer	PH, HT, HC	–	<1.0	35.4	Nifedipine	Pravastatin	Psl 15 mg/day
2	52	Myocardial infarction	PH, HT, HC, DM	+	<1.0	<1.2	Captopril/ benidipine	Probucol/ pravastatin	Psl 10 mg/day
3	50	Cerebral infarction	PH, SM, DM	+	<1.0	<1.2			Psl 15 mg/day
4	48	Cerebral infarction	PH	+	<1.0	<1.2			Psl 12.5 mg/day
5	42	External shunt failure	PH, HT, HC, DM	+	<1.0	<1.2	Nifedipine	Niceritol/ pravastatin	Bms 1.2 mg/day
6	39	Cerebral infarction	PH, HT	+	<1.0	56.9	Nilvadipine		Psl 15 mg/day
7	29	Miscarriage with thrombus of placenta	PH	+	<1.0	<1.2			Psl 8 mg/day
8	49	Myocardial infarction	PH	+	<1.0	<1.2			Bms 1.5 mg/day
9	35	Cerebral infarction	PH, HT	+	<1.0	<1.2	Benidipine		Bms 1.0 mg/day
10	39	Cerebral infarction	PH, DM	+	1.4	<1.2			Psl 10 mg/day
11	48	Pulmonary artery thromboembolism	PH, HT	+	<1.0	<1.2	Nifedipine		Psl 15 mg/day
12	56	Valvular thrombus formation	HT, HC	+	2.5	115	Nifedipine	Tocopherol nicotinate	Psl 15 mg/day

All patients had antithrombotic treatment with aspirin.

PH: past history of thrombotic events; HT: hypertension; HC: hypercholesterolemia; DM: diabetes mellitus; SM: smoking; LAC: lupus anticoagulant; aCLIgG: IgG anticardiolipin antibody; β2GPI-aCL: β2GPI dependent anticardiolipin antibody; Psl: prednisolone; Bms: betamethasone.

Table III. Incidence of new thrombotic events between patients with and without risk factor.

Risk Factor	Incidence of New Thrombosis (Events/Patients)		Odds Ratio	95% CI	p Value
	With Risk Factor	Without Risk Factor			
Risk factors					
PHTE	11/26 (42.3%)	1/140 (0.7%)	101.93	12.29–845.22	<0.0001
Hypertension	7/28 (25.0%)	5/138 (3.6%)	8.87	2.58–30.53	<0.001
Hypercholesterolemia	4/42 (9.5%)	8/124 (6.5%)	1.53	0.44–5.35	0.501
Obesity (BMI ≥ 25)	0/11 (0.0%)	12/155 (7.7%)	–	–	1.000
Smoking	1/28 (3.6%)	11/138 (8.0%)	0.43	0.05–3.45	0.412
Diabetes mellitus	4/17 (23.5%)	8/149 (5.4%)	5.42	1.44–20.46	<0.050
Antiphospholipid antibodies					
aCLIgG	2/20 (10.0%)	10/146 (6.8%)	1.51	0.31–7.45	0.640
β2GP1-aCL	3/21 (14.3%)	9/145 (6.2%)	2.52	0.62–10.17	0.181
LAC	11/40 (27.5%)	1/126 (0.8%)	47.41	5.88–382.03	<0.0001
Combination of antiphospholipid antibodies					
One of any aPLs	9/32 (28.1%)	3/134 (2.2%)	17.09	4.3–67.90	<0.0001
LAC and aCLIgG	2/13 (15.4%)	10/153 (6.5%)	2.6	0.51–13.37	0.239
LAC and β2GP1-aCL	2/11 (18.2%)	10/155 (6.5%)	3.22	0.61–16.96	0.183
aCLIgG and β2GP1-aCL	1/5 (20.0%)	11/161 (6.8%)	3.41	0.35–33.17	0.316
All 3 aPLs positive	1/3 (33.3%)	11/163 (6.7%)	6.91	0.58–82.28	0.203

PHTE: past history of thrombotic events; aCLIgG: IgG anticardiolipin antibody; β2GP1-aCL: β2GPI-dependent anticardiolipin antibody; LAC: lupus anticoagulant; aPLs: antiphospholipid antibodies; 95%CI: 95% confidence interval.

aPLs were thought to be major risk factors for thrombosis in patients with SLE.

According to a prospective study by Finazzi et al,[26] 12 of 69 (17.4%) patients with aPLs-positive SLE developed thrombosis, showing no significant differences between Finazzi's SLE cohort and those in our series (12 of 58, 20.7%; $p = 0.648$). On the other hand, Sebastiani et al[27] reported a multiinstitutional study of 574 European patients with SLE and aCL and β2GP1-aCL. In their study, it was noted that 21 of 81 (25.9%) patients with aCLIgG and 26 of 110 (23.6%) patients with β2GP1-aCL had PHTE. In our study, 6 of 20 patients with aCLIgG (30.0%; $p = 0.780$) and 7 of 21 patients with β2GP1-aCL (33.3%; $p = 0.412$) had a PHTE, and there were no statistically meaningful differences from Sebastiani's cohort. Therefore, there were no differences in the incidence of thrombotic events and PHTE between Japanese and European patients with SLE and aPLs.

In this study, SLE patients with PHTE (42.3%; $p < 0.0001$), hypertension (25.0%; $p < 0.001$), and DM (23.5%; $p < 0.05$) had significantly higher morbidity of thrombosis than those without these risks (Table III).

Table IV. Odds ratio by logistic regression model.

Variable	Regression Coefficient	Odds Ratio	95% CI
PHTE	3.41	30.19	1.33–683.13
Hypertension	2.74	15.44	1.77–134.80
LAC	2.65	14.11	0.48–412.42
Diabetes mellitus	2.45	11.53	0.83–159.94

PHTE: past history of thrombotic events; LAC: lupus anticoagulant; 95%CI: 95% confidence interval.

Table V. Odds ratio of combination of 2 risk factors.

Risk Factors	Combination of Risk Factors			
	Single Risk Factor OR (95%CI)	PHTE OR (95%CI)	Hypertension OR (95%CI)	Diabetes Mellitus OR (95%CI)
LAC positive	47.4 (5.9–382.0)	54.2 (10.7–274.3)	76.0 (12.6–458.0)	NC
Diabetes mellitus	5.4 (1.4–20.5)	NC	7.5 (1.2–46.0)	–
Hypertension	8.9 (2.6–30.5)	76 (12.6–458.0)	–	–
PHTE	101.9 (12.3–845.2)	–	–	–

PHTE: past history of thrombotic events; LAC: lupus anticoagulant; OR: odds ratio; 95%CI: 95% confidence interval; NC: not calculable (because the datum of a column of 2×2 contingency table is 0).

Among aPLs, only LAC (27.5%; $p < 0.0001$) had a high morbidity of thrombosis, but not aCLIgG (10.0%; $p = 0.640$) and β2GPI-aCL (14.3%; $p = 0.181$). From this result, it appears that LAC has a greater predictive value for thrombosis in patients with SLE compared to that of other aPLs.

Hypertension and DM are also factors that accelerate atherosclerosis. Atherosclerosis is an important cause of arterial thrombosis. Factors contributing to the atherosclerotic process include oxidized low-density lipoprotein (LDL), lipoprotein (a), fibrinogen, and von Willebrand factor. The observations that aCL cross-reacts with antibodies to oxidized LDL[28] and that plasma concentrations of lipoprotein (a)[29] and von Willebrand factor[30] are abnormally elevated in some patients with aPLs make a link with atherosclerosis very likely. It has also been reported that aPLs accelerate atherosclerosis and may be causes of both hypertension[31] and atherosclerosis,[28,32-35] but there is no clinical evidence supporting this hypothesis. From the multivariate regression analysis, the adjusted odds ratios of hypertension and LAC were almost the same, and therefore, we consider that hypertension is the same potent risk factor as LAC in the development of thrombosis in patients with SLE (Table IV). PHTE showed the highest adjusted odds ratio (30.19) among 4 predictive variables. When the odds ratio of the combination of 2 risk factors for the development of thrombotic events was compared, the combination of hyper-

tension and LAC showed statistically meaningful higher odds ratios than these risk factors alone. These results suggest that a combination of these predictive variables increases the risk for the development of thrombosis.

In conclusion, the incidence of thrombosis was not different between European cohorts and our Japanese cohort, and PHTE, hypertension, LAC, and DM are important risk factors for the development of new thrombosis in patients with SLE.

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血管炎症候群

顕微鏡的多発血管炎

Microscopic polyangiitis

橋本博史

Key words：顕微鏡的多発血管炎，MPO-ANCA，急速進行性腎炎，間質性肺炎，免疫抑制療法

1. 概　　念

侵される血管の大きさによる原発性血管炎の分類がJennetteらにより1994年に提唱された[1]．この分類により顕微鏡的多発血管炎(microscopic polyangiitis: MPA)が結節性多発動脈炎(polyarteritis nodosa: PN)より分離独立された．これはMPAがPNに比べより小さな血管を侵し，かつ抗好中球細胞質抗体(antineutrophil cytoplasmic antibody: ANCA)が陽性を示すことによる．ANCAには，proteinase 3(PR3)-ANCAに代表されるcytoplasmic-ANCA(cANCA)とmyeloperoxidase(MPO)-ANCAに代表されるperinuclear-ANCA(pANCA)が含まれるが，MPAは，主にMPO-ANCA陽性を示し，半月体形成性腎炎による急速進行性腎炎と間質性肺炎を来しやすい．高齢者に多く発症し予後不良である．

2. 病因・病態

MPAの原因はいまだ不明であるが，HLAとの関係では，MPO-ANCA陽性を示すMPAはHLA-DRB1*0901(DR9)と有意の相関を認める($p=0.001$, $Pc=0.022$, odds' ratio 2.96)[2]．DRB1*0901との関連は，MPA以外の疾患を含めたpANCA陽性患者においても認められる．

環境因子では，血管炎の発症に微生物のスーパー抗原の関与も示唆されている．スーパー抗原は血管障害をもたらす自己反応性のT細胞活性化や，ANCA，抗血管内皮細胞抗体などを産生する自己反応性のB細胞の活性化をもたらす可能性がある．スーパー抗原とTCRVβ遺伝子の解析が検討されているが，MPAでは，TCRVβ-2.1，Vβ3，Vβ9，Vβ13，Vβ14，Vβ15，Vβ24遺伝子ファミリーが有意に多く用いられ，12例中6例にPCRでオリゴクローナルバンドが認められている[3]．血管炎に特異的なクローンは同定されていないが，MPAがスーパー抗原関連疾患であることを示唆している．また，硅肺症や粉塵もしばしば発症の契機となり，阪神淡路大震災では，ある医療機関で震災後3年以内に15例のMPO-ANCA関連血管炎の発症を認め，それ以前の症例に比べ短期間に集中し重篤な肺・腎病変を認めている．震災に伴う粉塵が高率に上気道病変をもたらし発症したことを示唆している[4]．また，ヒドララジン，プロピルチオウラシル，ペニシラミン，オメプラゾールなどの薬剤誘発性のMPO-ANCA血管炎も知られている．

病態発症機序に関してはANCAとサイトカインの関与が強く示唆されている(図1)[5]．遺伝的要因を背景に何らかの感染を契機として単球，好中球，マクロファージを含む炎症性細胞や免疫担当細胞が活性化し，TNFαやIL-1βなどの

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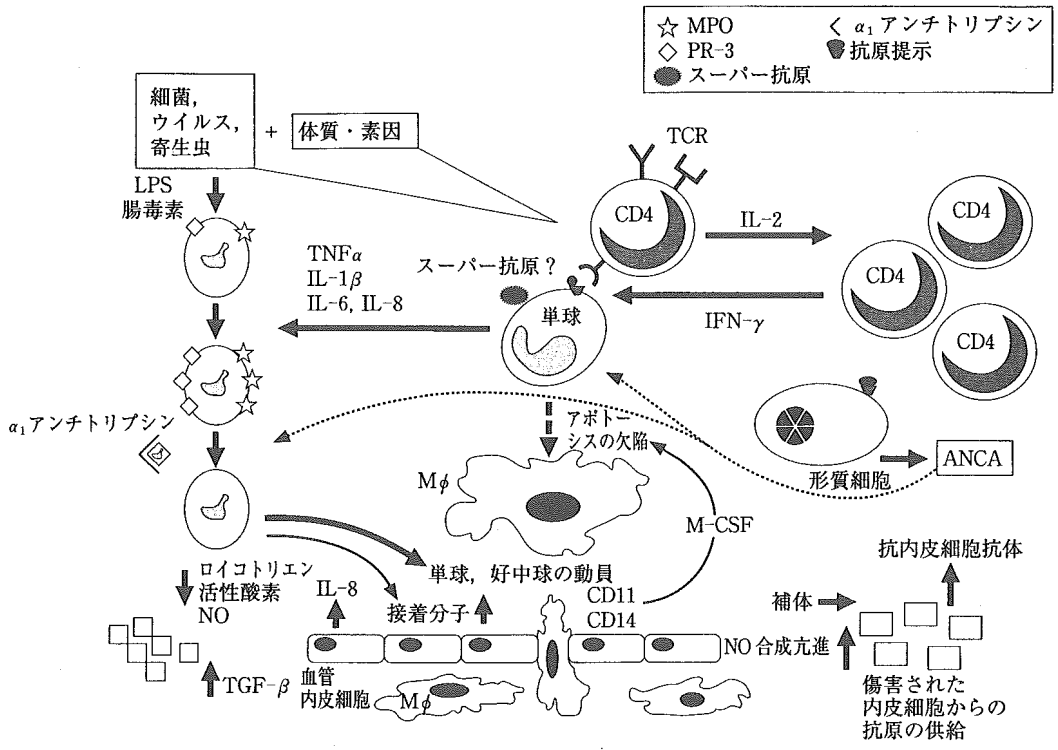

図1 血管炎の発症機序[5]

サイトカイン産生をもたらし，接着分子の発現により炎症性細胞と血管内皮細胞の接着，浸潤が促進する．刺激を受けた好中球の表層上にはプロテアーゼが過剰発現し，ANCAの産生に寄与するとともに流血中のANCAの標的ともなり活性化し，脱顆粒を惹起し血管内皮細胞傷害をもたらす．血管内皮細胞より産生されるM-CSFはマクロファージの傷害部位への浸潤につながるが，MRL/lprマウスのごとくFasを介したアポトーシスの欠陥がみられればマクロファージの活性化により肉芽腫性血管炎の病態につながる可能性がある[6]．ロイコトリエン，活性酸素，NOなどの放出もECを傷害し血管透過性亢進につながる．

MPO-ANCAが直接組織障害にかかわっているかどうかが動物モデルで検討されている．MPOで免疫したMPOノックアウトマウスの脾細胞をT/B細胞機能不全マウスに移入し，移入された脾細胞の用量依存性に壊死性半月体形成性腎炎，肉芽腫性炎，全身性壊死性血管炎を認め，更に，IgG抗MPO-ANCAを移入した場合においても，寡免疫複合体性糸球体壊死と半月体形成性腎炎を認めている[7]．

3. 臨床症状

a. 初発症状

発熱や体重減少，関節痛，筋肉痛などの全身症状とともに急速進行性腎障害，呼吸困難などをみる．MPAの初発症状を**表1**に示す[8]．

b. 臨床症状

発熱，体重減少，関節痛(炎)，筋肉痛(炎)などとともに壊死性半月体形成性腎炎による急速進行性腎炎と間質性肺炎・肺出血の2臓器症状(肺・腎症候群)を認める(**図2**)．腎限局型，肺限局型も存在する．その他の血管炎症候では，紫斑・出血や網状青色皮斑などの皮膚症状，多発性単神経炎，消化管出血などをみる．**表2**に臨床症状を示す．

表1 MPAの初発症状(n=63)

	(例)	(%)		(例)	(%)
全身症状	45	71.4	リベドー	3	4.8
発 熱	34	54.0	紫斑・出血斑	7	11.1
体重減少	13	20.6	レイノー現象	2	3.2
リンパ節腫大	2	3.2	関節・筋症状	37	58.7
浮 腫	13	20.6	関節痛(炎)	29	46.0
精神神経症状	15	23.8	筋肉痛(炎)	22	34.9
多発性単神経炎(運動障害あり)	4	6.3	筋力低下	6	9.5
多発性単神経炎(運動障害なし)	9	14.3	眼症状	5	7.9
皮膚症状	12	19.0	視力障害	2	3.2
皮膚潰瘍・梗塞	2	3.2	上強膜炎	3	4.8
皮下結節	2	3.2	虹彩炎	3	4.8
紅 斑	4	6.3			

4. 検査所見

検査(表3)では，赤沈亢進，CRP陽性，白血球増加，尿蛋白，赤血球尿，白血球尿，円柱尿，腎機能低下，MPO-ANCA/P-ANCA陽性(50-80%)をみる．組織生検による病理組織学的検査所見では，細動脈，毛細血管，後毛細血管細静脈の壊死性血管炎と炎症性細胞浸潤を認める．腎では，半月体形成性腎炎，壊死性糸球体腎炎，壊死性血管炎などをみる(図2)．

5. 診　　断

診断は，上記の特徴的な臨床症状と検査所見による．厚生労働省調査研究班より診断基準(表4)が提唱されている．PNと他のANCA関連血管炎の疾患との鑑別を要する．PNとの鑑別点を表5に示す．

6. 治療・予後

治療は，ステロイド薬と免疫抑制薬が主たる治療薬である．全身型の場合には，寛解導入療法としてプレドニゾロン(prednisolone: PSL) 0.6-1mg/kg/日とシクロホスファミド(cyclophosphamide: CP) 0.5-2mg/kg/日の併用で治療開始する．ときに，ステロイドのパルス療法を先行させることもある．また，CPは間欠大量静注療法(IVCP，500-750mg/回/1-3カ月ごと)として用いられることもある．上記治療を3-4週間継続投与後，臨床症状，炎症反応，臓器障害，ANCAなどを指標にPSLを漸減する．CPが使用できない場合にはアザチオプリン(azathioprine: AZ)を用いる．そのほか，病態に応じ血漿交換療法やγグロブリン大量療法などが試みられることがある．寛解維持ないし寛解後の再燃防止，薬剤副作用軽減，感染症併発のリスクを減らすためにCPに代えてAZ，メトトレキサート(methotrexate: MTX)，シクロスポリン(cyclosporin: CYA)などが用いられるが，CYAは腎毒性があり腎機能に留意する．病態に応じ血液透析や人工呼吸管理を行う．図3に，MPAを含むANCA関連血管炎の治療指針を示す[9]．

予後は不良で，特に診断後1年以内の死亡率が高い．感染症の合併率が高く(46%)，主たる死因は感染症，肺出血，腎不全である．

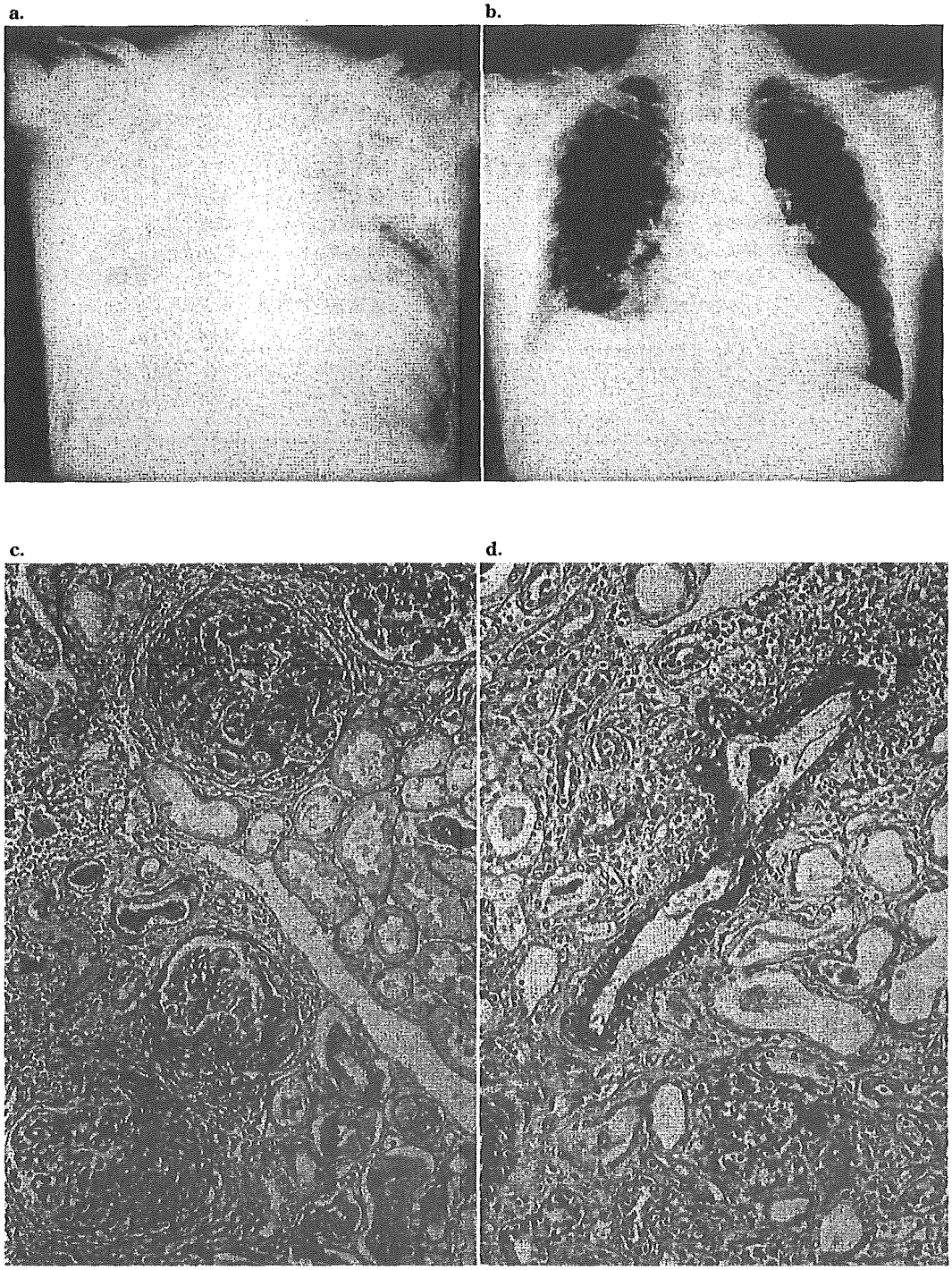

図2 MPAにみられた肺・腎症候群
a: 肺出血像，b: 間質性肺炎，c: 半月体形成性腎炎，壊死性糸球体腎炎，d: 壊死性血管炎.

表2 MPAの臨床症状(n=63)

	(%)		(%)
全身症状	88.9	心外膜炎	3.2
精神神経症状	47.6	呼吸器症状	63.5
多発性単神経炎(運動障害あり)	15.9	気管支喘息	4.8
多発性単神経炎(運動障害なし)	30.0	間質性肺炎	33.3
皮膚症状	42.9	肺出血	22.2
関節・筋症状	76.2	肺浸潤	25.4
眼症状	15.9	腎症状	87.3
耳鼻咽喉症状	15.9	急速進行性腎炎	66.7
心症状	20.6	腎不全	49.2

表3 MPAの検査所見(n=63)

	(%)		(%)
白血球増加	76	高IgE血症	20
血小板増加	31	リウマトイド因子陽性	44
好酸球増加	17	抗核抗体陽性	33
赤沈亢進	81	蛋白尿	93
CRP陽性	90	赤血球尿	77
高クレアチニン血症	75	細胞性円柱	60
高γ-グロブリン血症	52		

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表4 顕微鏡的多発血管炎の診断基準(厚生省難治性血管炎分科会，1998年修正)

1. 診断基準項目
   1) 主要症候
      (1) 急速進行性糸球体腎炎
      (2) 肺出血，もしくは間質性肺炎
      (3) 腎・肺以外の臓器症状
          紫斑，皮下出血，消化管出血，多発性単神経炎など
   2) 主要組織所見
      細動脈，毛細血管，後毛細血管細動脈の壊死，血管周囲の炎症性細胞浸潤
   3) 主要検査所見
      (1) MPO-ANCA陽性
      (2) CRP陽性
      (3) 蛋白尿・血尿，BUN，血清クレアチニン値の上昇
      (4) 胸部X線所見：浸潤陰影(肺胞出血)，間質性肺炎
2. 判定基準
   1) 確実(definite)
      (a) 主要症候の2項目以上を満たし，組織所見が陽性の例
      (b) 主要症候の(1)および(2)を含め2項目以上を満たし，MPO-ANCAが陽性の例
   2) 疑い(probable)
      (a) 主要症候の3項目を満たす例
      (b) 主要症候の1項目とMPO-ANCA陽性の例
3. 鑑別診断
      (1) 古典的PN
      (2) ウェゲナー肉芽腫症
      (3) アレルギー性肉芽腫性血管炎(チャーグ・ストラウス症候群)
      (4) グッドパスチャー症候群
4. 参考事項
      (1) 主要症候の出現する1-2週間前に先行感染(多くは上気道感染)を認める例が多い．
      (2) 主要症候(1)，(2)は約半数例で同時に，その他の例ではいずれか一方が先行する．
      (3) 多くの例でMPO-ANCAの力価は疾患活動性と平行して変動する．
      (4) 治療を早く中止すると，再発する例がある．

表5 PNとMPAの特徴

特 徴	結節性多発動脈炎 (古典的PN)	顕微鏡的多発血管炎 (顕微鏡的PN)
病理所見		
血管炎のタイプ	壊死性動脈炎	壊死性血管炎
侵襲血管のサイズ	中・小筋型動脈 ときに細動脈	小血管(毛細血管，細動静脈) ときに小動脈
臨床所見		
急速進行性腎炎	ま れ	多 い
高血圧	多 い	ま れ
肺出血	ま れ	多 い
間質性肺炎	ま れ	あ り
再 発	ま れ	あ り
MPO-ANCA	陰 性	陽 性
動脈造影(小動脈瘤，狭窄)	あ り	な し
確定診断	動脈造影	生 検

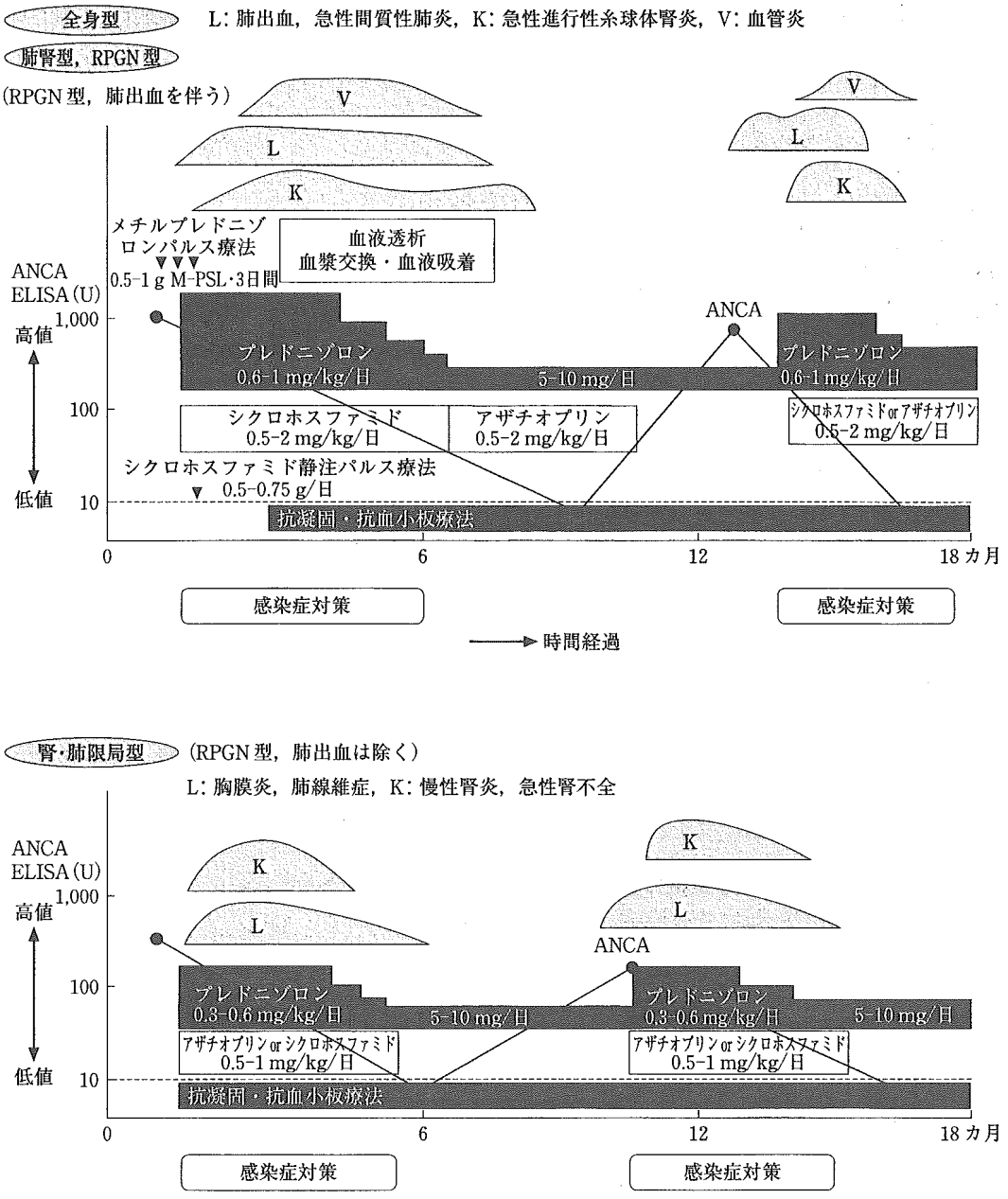

図3 ANCA関連血管炎に対する病型別免疫抑制治療(2001年)