Table 1 Correspondence of the variant by Columbia classification to the category determined by dominant location/quality factor

Columbia classification (number of cases)	Dominant location/quality factor (number of cases)
COL (13)	TIP-C (2)
	NOS-C (4)
	NOS-F/C (5)
	PH-F/C (2)
TIP (24)	TIP-C (18)
	TIP-F/C (3)
	NOS-F/C (1)
	NOS-F (2)
CEL (11)	NOS-C (5)
	NOS-F/C (6)
PH (13)	PH-F (13)
NOS (19)	NOS-F/C (1)
	NOS-F (18)

COL collapsing variant, *TIP* tip variant, *CEL* cellular variant, *PH* perihilar variant, *NOS* not otherwise specified variant, *C* cellular, *F/C* fibrous/cellular, and *F* fibrous

NOS fibrocellular, and two of NOS fibrous. Among the 11 cases of the CEL variant, there were five NOS cellular cases and six NOS fibrocellular cases. All 13 cases of the PH variant were categorized as PH fibrous. Nearly all of the 19 cases of the NOS variant were categorized as NOS fibrous (18), with one NOS fibrocellular case.

Baseline clinical findings and outcomes

A comparison of the baseline clinical findings among the FSGS variants is presented in Table 2. The histological variants showed significant differences in the mean interval between discovery of proteinuria and biopsy and in the mean levels of sCr, serum albumin (sAlb), and urinary protein excretion at the time of the kidney biopsy (Table 2). The mean interval between discovery of proteinuria and biopsy was shortest for the TIP variant (7.8 ± 2.3 months), followed by the CEL (18.7 ± 5.4 months) and COL variants (41.6 ± 16.2 months), with considerably longer times for the NOS (89.0 ± 5.4 months) and PH variants (136.0 ± 27.7 months). The sCr level at biopsy was highest in the COL variant (2.04 ± 0.54 mg/dl), followed by the CEL variant (1.58 ± 0.18 mg/dl). The sAlb level at biopsy was lowest in the CEL variant (2.84 ± 0.32 g/dl) and TIP variant (2.88 ± 0.20 g/dl), followed by the COL variant (3.07 ± 0.31 g/dl). Proteinuria at biopsy was high in the CEL (8.9 ± 2.3 g/day), TIP (8.8 ± 2.3 g/day), and COL variants (7.1 ± 2.6 g/day), and was relatively low in the NOS (1.7 ± 0.5 g/day) and PH variants (2.1 ± 0.5 g/day). The prevalence of nephrotic syndrome was highest in TIP (72.7%) and CEL (72.7%) variants, followed by the COL variant (46.2%), and much lower in PH (16.7%) and NOS (11.1%) variants.

The therapeutic modalities and outcomes among the variants are shown in Table 3. Steroids were usually administered, either alone or combined with immunosuppressive agents, in the COL (72.8%), TIP (86.3%), and CEL (70%) variants. Angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) were frequently administered to all variants (41/75, 52.4%), and ACEI/ARB administration without steroids was preferred in the PH variant (84.6%). LDL apheresis was performed in two of the CEL cases and in one of the COL and TIP cases, to treat severe dyslipidemia. Sixty-six cases were followed and their outcomes were evaluated. Persistent proteinuria was evident in all variants; however, at final observation, the proteinuria levels were low and showed no difference among the variants. Additionally, the sCr level at the final evaluation did not differ among the variants, probably due to the small number of cases and the relatively short period of observation (55.9 ± 8.8 months). The rate of remission was higher in the TIP (82.2%) variant than in the other variants [CEL (60%), NOS (47.1%), COL (44.4%), and PH (30%)]. Twelve of the 66 cases (18.2%) progressed to ESRD and began HD. These included two of the 19 cases with the TIP variant (10.5%), and relatively higher percentages of those with COL (3/10, 30%) and CEL variants (3/9, 33.3%), with no significant difference between the last two. No patient with PH progressed to ESRD.

Histological findings

Histological findings in a total of 1,299 glomeruli were assessed in the biopsy specimens of the 80 patients (Table 4). Among these, 207 glomeruli (15.9%) were globally sclerotic, and 210 (16.2%) were segmentally sclerotic, with an average of

Table 2 Baseline clinical characteristics of 80 FSGS patients categorized by Columbia classification

Case number	All	COL	TIP	CEL	PH	NOS	ANOVA or Ryan's test *P*-value	Multiple comparison (Sheffe) $P < 0.05$
	80	13 (16.2%)	24 (30%)	11 (13.8%)	13 (16.2%)	19 (23.8%)		
Age	39.4 ± 1.7	39.9 ± 4.1	42.1 ± 3.8	44.1 ± 5.3	38.1 ± 12.9	34.1 ± 2.9	ns	
Male/female	45/35	9/4	9/15	7/4	9/4	11/8	ns[*1]	
Interval to Bx (M)	57.6 ± 8.8	41.6 ± 16.2	7.8 ± 2.3	18.7 ± 5.4	136.0 ± 27.7	89.0 ± 5.4	<0.0001	PH vs. COL, TIP, CEL; NOS vs. TIP, CEL
sCr (mg/dl)	1.37 ± 0.11	2.04 ± 0.54	1.16 ± 0.11	1.58 ± 0.18	1.08 ± 0.05	1.22 ± 0.09	0.033	ns
sAlb (mg/dl)	3.34 ± 0.11	3.07 ± 0.31	2.88 ± 0.20	2.84 ± 0.32	4.11 ± 0.09	3.87 ± 0.10	<0.0001	TIP vs. NOS, PH; CEL vs. NOS, PH
U-p (d/day)	5.7 ± 0.9	7.1 ± 2.6	8.8 ± 2.0	8.9 ± 2.3	2.1 ± 0.5	1.7 ± 0.5	0.0051	TIP vs. NOS
N. synd.	34/76 (44.7%)	6/13 (46.2%)	16/22 (72.7%)	8/11 (72.7%)	2/12 (16.7%)	2/18 (11.1%)	<0.0001[*1] (TIP vs. NOS) 0.0012[*1] (CEL vs. NOS)	

Bx biopsy, *M* month, *sCr* serum creatinine, *sAlb* serum albumin, *U-p* urinary protein, *COL* collapsing variant, *TIP* tip variant, *CEL* cellular variant, *PH* perihilar variant, *NOS* not otherwise specified variant, and *N. synd* Nephrotic syndrome

Nephrotic syndrome was defined as urinary protein excretion (U-p): ≥ 3.0 g/day; ns, not significant

Quantitative variables are mean ± standard error; [*1]: by Ryan's test

2.63 ± 0.20 segmentally sclerotic glomeruli per biopsy specimen. The percentage of global glomerular sclerosis (%GS) differed significantly among variants ($P = 0.036$), with higher values for the NOS (23.6 ± 5.1%) and COL variants (21.1 ± 5.9%), followed by the CEL (17.5 ± 4.1%) and PH variants (16.8 ± 2.9%), and then the TIP variant (8.0 ± 2.3%). However, the percentage of segmental glomerular sclerosis (%SS) was not significantly different among the variants. The total percentage of GS plus SS (%GS + SS) differed significantly among the variants ($P = 0.0105$), with higher values for the COL (41.9 ± 6.1%), CEL (42.2 ± 5.5%), and NOS variants (42.2 ± 5.2%), followed by the PH variants (32.8 ± 4.0%) and the TIP variants (25.1 ± 2.7%). The IF/TA score also differed significantly among the variants ($P = 0.0106$); the CEL variant had the highest score (2.10 ± 0.27), followed by the NOS (1.79 ± 0.18), COL (1.62 ± 0.26), and PH variants (1.54 ± 0.18), with the TIP variant having the lowest score (1.04 ± 0.16).

Heterogeneity of segmental lesions in each histological variant

All glomeruli with segmental sclerosis were independently evaluated in terms of location and quality of the segmental lesions. The histological characteristics of segmental lesions in terms of location and quality factor are presented in Fig. 3. Segmental lesions were localized as TIP (Fig. 3a, b), PH (Fig. 3f) or NOS (Fig. 3c, d, e). Cellular segmental lesions were characterized by a proliferation of glomerular epithelial cells (Fig. 3a, c, d) and/or intracapillary occlusion with hypercellularity, including foam cells and infiltrated leukocytes (Fig. 3a, d). Fibrous lesions showed consolidation (sclerosis) of the glomerular tuft with increased extracellular matrix (Fig. 3b, e, f). Hyalinosis was observed in both cellular and fibrous lesions (Fig. 3f). The 210 glomerular segmental lesions consisted of 57 (27%) cellular TIP, four (2%) fibrous TIP, 42 (20%) cellular NOS, 86 (41%) fibrous NOS, and 21 (10%) fibrous PH lesions (Fig. 4). The majority of segmental lesions in the TIP area were cellular (57/62, 93.4%), and only a small percentage were fibrous (5/62, 8.1%). In contrast, all 21 segmental lesions in the PH area were fibrous. The segmental lesions in

Table 3 Therapeutic modalities and outcomes of 80 FSGS patients categorized by Columbia classification

Case number	All 80	COL 13 (16.2%)	TIP 24 (30%)	CEL 11 (13.8%)	PH 13 (16.2%)	NOS 19 (23.8%)	ANOVA or Ryan's test *P*-value
Steroid only	24/75 (32%)	3/11 (27.3%)	14/22 (63.6%)	4/10 (40%)	0/13 (0%)	3/19 (15.8%)	0.0001^{*1} (TIP vs. PH) 0.0017^{*1} (TIP vs. NOS)
Steroid + IS	15/75 (20%)	5/11 (45.5%)	5/22 (22.7%)	3/10 (30%)	0/13 (0%)	2/19 (10.5%)	ns^{*1}
ACEI/ARB only	24/75 (32%)	3/11 (27.3%)	2/22 (9.1%)	2/10 (20%)	11/13 (84.6%)	6/19 (31.6%)	$<0.0001^{*1}$ (TIP vs. PH) 0.0018^{*1} (CEL vs. PH) 0.005^{*1} (COL vs. PH) 0.0032^{*1} (NOS vs. PH)
LDL apheresis	7/75 (9.3%)	1/11 (9.1%)	2/22 (9.1%)	4/10 (40%)	0/13 (0%)	0/19 (0%)	0.0011^{*1} (CEL vs. PH) 0.0012^{*1} (CEL vs. NOS)
F/u number of pts	66	10	19	9	10	18	
F/u duration (m)	55.9 ± 8.8	47.1 ± 12.7	79.3 ± 14.0	52.6 ± 11.8	50.9 ± 13.1	38.0 ± 7.8	ns
Final U-p (g/day)	0.97 ± 0.16	1.6 ± 0.5	0.6 ± 0.3	0.9 ± 0.4	0.9 ± 0.2	1.0 ± 0.3	ns
Remission (%)	37/65 (56.9%)	4/9 (44.4%)	16/19 (84.2%)	6/10 (60%)	3/10 (30%)	8/17 (47.1%)	ns^{*1}
Final sCr (mg/dl)	2.83 ± 3.70	4.00 ± 1.34	1.80 ± 0.61	4.84 ± 1.80	1.19 ± 0.10	2.73 ± 0.70	ns
HD (%)	12/66 (18.2%)	3/10 (30%)	2/19 (10.5%)	3/9 (33.3%)	0/10 (0%)	4/18 (22.2%)	ns^{*1}

COL collapsing variant, *TIP* tip variant, *CEL* cellular variant, *PH* perihilar variant, *NOS* not otherwise specified variant, *IS* immunosuppressant such as cyclosporine or cyclophosphamide, *ACEI* Angiotensin converting enzyme inhibitors, *ARB* Angiotensin II Receptor Blocker, *ACEI/ARB* only, the patients treated with ACEI or ARB without other therapies (steroid or IS), *F/u* follow up; remission was defined as a reduction of proteinuria less than 0.5 g/day after treatment, *HD* hemodialysis, *ns* not significant

Quantitative variables are mean ± standard error; ^{*1}: by Ryan's test

Table 4 Comparison of histological findings of 80 FSGS patients categorized by Columbia classification

	All	COL	TIP	CEL	PH	NOS	ANOVA *P* value	Multiple comparison (Sheffe) $P < 0.05$
% GS	16.6 ± 1.9	21.1 ± 5.9	8.0 ± 2.3	17.5 ± 4.1	16.8 ± 2.9	23.6 ± 5.1	0.0361	ns
% SS	18.9 ± 1.3	20.8 ± 3.7	17.1 ± 2.0	24.7 ± 5.2	16.0 ± 13.0	18.6 ± 2.3	ns	
% GS + SS	35.3 ± 2.1	41.9 ± 6.1	25.1 ± 2.7	42.2 ± 5.5	32.8 ± 4.0	42.2 ± 5.2	0.0105	ns
IF/TA score (0–3)	1.53 ± 0.10	1.62 ± 0.26	1.04 ± 0.16	2.10 ± 0.27	1.54 ± 0.18	1.79 ± 0.18	0.0106	CEL vs. TIP

Gl glomerular, *GS* global sclerosis, *SS* segmental sclerosis, *IF/TA* interstitial fibrosis and tubular atrophy
Quantitative variables are mean ± standard error of mean

the NOS area were either cellular (42/127, 33.1%) or fibrous (86/127, 66.9%).

The location heterogeneity of segmental lesions in each histological variant is shown in Fig. 5. The different degrees of heterogeneity were probably associated with the diagnostic hierarchy of the Columbia classification, which validated the diagnostic priority in the order COL, TIP, CEL, PH, and NOS. In the COL variant, segmental lesions were located in the TIP (12/51, 23.5%), NOS (36/51, 70.6%), and PH areas (3/51, 5.9%). In the TIP variant, segmental lesions were located in the TIP (49/75, 65.3%) and NOS areas (26/75, 34.7%), but not in the PH area. Half of the patients with the TIP variant (12/24, 50%) had segmental lesions located in the NOS area, but the dominant location of the segmental lesions was in the TIP area in 21/24 (87.5%) cases (Table 1). All of the segmental lesions in CEL variants were located in the NOS area (28/28, 100%). The majority of the segmental lesions in PH variants were located in the PH area (18/21, 85.7%), with only three (14.3%) in the NOS area. Among the 13 patients with the PH variant, three patients (23.1%) had segmental lesions in the NOS area, but the PH area in all PH variants was the dominant location of the segmental lesions (Table 1). All NOS variant segmental lesions were located in the NOS area (35/35, 100%).

The quality heterogeneity of segmental lesions in each histological variant is shown in Fig. 6. Of the 51 COL variant segmental lesions, 32 (62.7%) were cellular, and 19 (37.3%) were fibrous. The cellular subtype was also predominant for the TIP (51/75, 68%) and CEL variants (16/28, 57.1%). In contrast, all segmental lesions of the NOS and PH variants were fibrous.

Overlap of histological findings in COL and CEL variants

Overlap of CEL lesions in the COL variants occasionally made it difficult to determine the variant. Because the Columbia classification defines the COL variant as "at least one glomerulus with segmental or global collapse with overlying podocyte hypertrophy and hyperplasia" [3], CEL lesions, defined as endocapillary hypercellularity occluding lumina with or without foam cells and karyorrhexis, can occasionally be admitted in the COL variant (Fig. 7). The coexistence of CEL lesions in the COL variants were observed in 9 of 13 COL cases (Supplemental Table 1). Although proteinuria tended to be higher in the COL variants with CEL lesions, no significant difference was demonstrated.

Dominant location/quality factors of segmental lesions correlation with clinical findings

Figure 8 compares clinical parameters according to the dominant location and quality factor of each case. With respect to predominant lesion location, the mean interval between symptom onset and biopsy was significantly shortest for patients with lesions predominantly in the TIP location (4.8 ± 1.1 months), followed by the NOS location (52.5 ± 10.1 months), and the interval was longest for the PH location (137.9 ± 24.1 months). With respect to predominant quality factor, the mean interval was shortest for patients with lesions of the cellular subtype (5.7 ± 1.0 months), longer for the fibrocellular subtype (40.8 ± 12.1 months), and longest for the fibrous subtype (105.0 ± 15.4 months; Fig. 8a). Proteinuria at biopsy was highest for patients with the

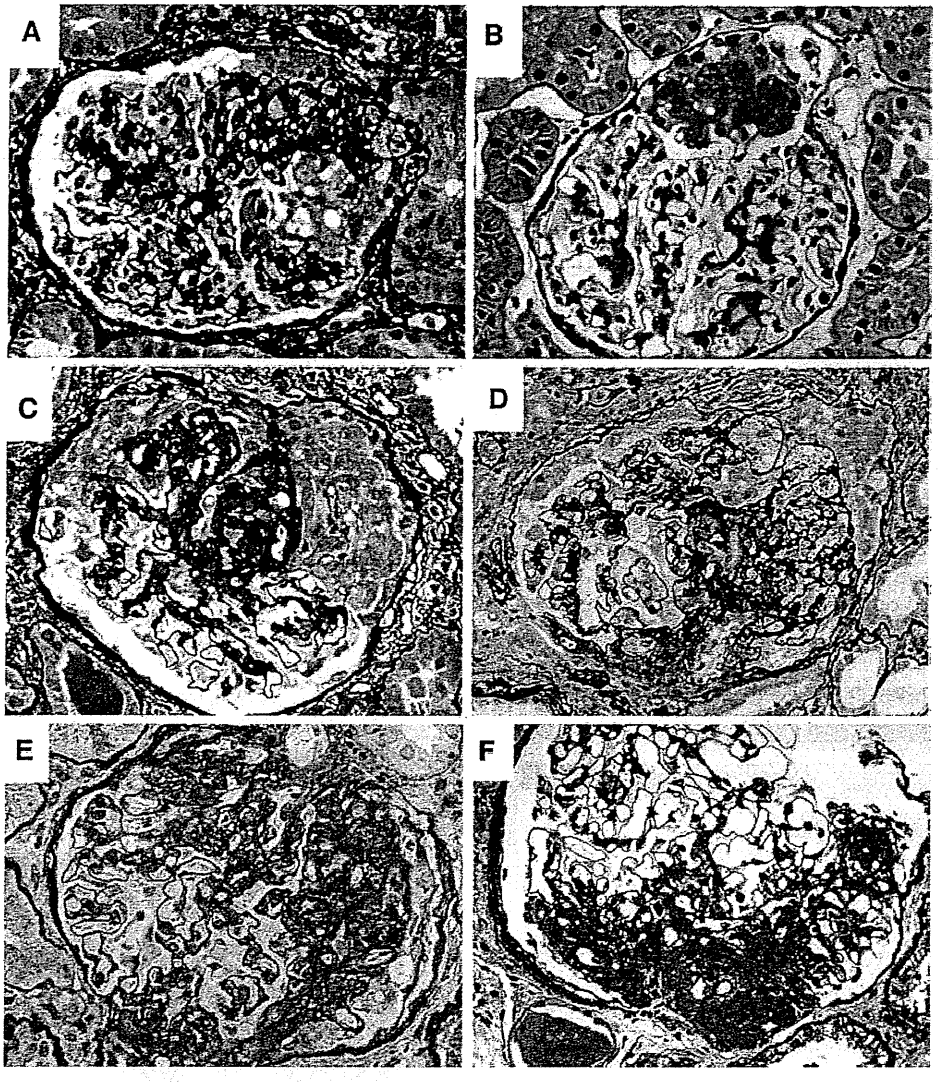


Fig. 3 Typical glomerular findings of segmental lesions regarding location and histological features. **a** TIP-located lesion with cellular histology (TIP-cellular). There is segmental accumulation of endocapillary foam cells involving the peripheral glomerular segment at the tubular pole. Podocytes overlying the segmental lesion are hypertrophic and hyperplastic. The histological variant of this glomerulus corresponds to TIP in the Columbia classification (silver methenamine stain, ×100). **b** TIP-located lesion with fibrous histology (TIP-fibrous). The glomerular tufts are collapsed with segmental accumulation of extracellular matrix involving the peripheral glomerular segment at the tubular pole. Podocytes overlying the segmental lesion are slightly proliferative. The histological variant of this glomerulus also corresponds to TIP in the Columbia classification. As a TIP-cellular lesion co-existed in the same specimen, the histological category of this case was deemed TIP-fibrocellular (F/C) (PAS stain, ×100). **c** Extensive segmental lesion in the NOS area with cellular histology (NOS-cellular). The glomerulus shows extensive collapse and obliteration of the glomerular tufts, accompanying prominent hypertrophy and hyperplasia of the overlying glomerular epithelial cells. This case is categorized as NOS-cellular and classified as a COL variant in the Columbia classification (silver methenamine stain, ×100). **d** Segmental lesion in the NOS area with active endocapillary cellular histology (NOS-cellular). Endocapillary accumulation of foam cells and leukocytes occluding the glomerular capillary lumina is regarded as an active histological feature of glomerular segmental lesions. This case is categorized as NOS-cellular and classified as a CEL variant in the Columbia classification. In addition to endocapillary proliferation, collapsing glomerular tufts may also be observed in some areas of the segmental lesion, making it difficult to differentiate between the COL and CEL variants (silver methenamine stain, ×100). **e** NOS-located lesion with a predominantly fibrous appearance (NOS-fibrous). Extensive segmental sclerosis is observed involving the NOS area, but at neither the vascular nor tubular pole. No cellular proliferation is seen in the segmental lesion. The case is categorized as NOS-fibrous and classified as NOS in the Columbia classification (PAS stain, ×100). **f** PH-located lesion showing segmental occlusion of the glomerular capillaries by fibrous matrix accumulation and hyalinosis around the glomerular hilum (PH-fibrous). Neither epithelial hyperplasia nor endothelial proliferation is seen in this glomerulus. This case is categorized as PH-fibrous and classified as the PH variant in the Columbia classification (PAS stain, ×100)

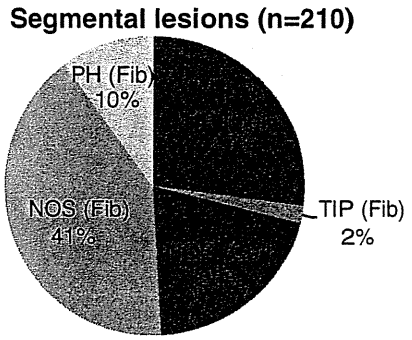
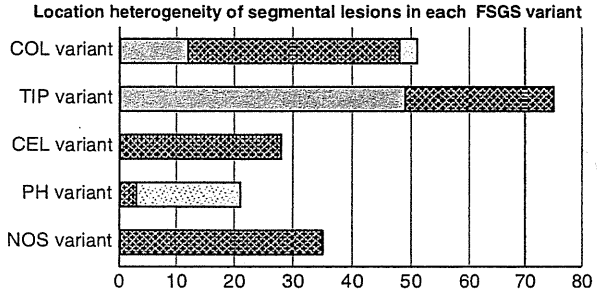


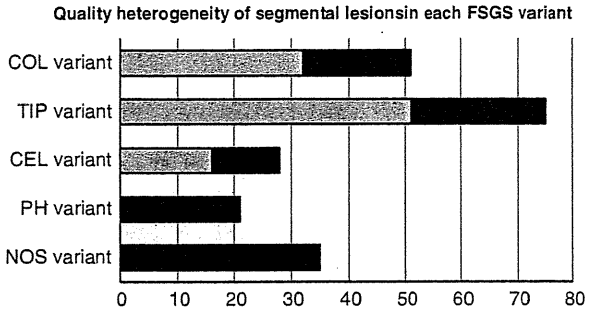
Fig. 4 Composition of location and quality factors in all segmental lesions ($n = 210$). The 210 glomerular segmental lesions consisted of 57 (27%) cellular TIP, four (2%) fibrous TIP, 42 (20%) cellular NOS, 86 (41%) fibrous NOS, and 21 (10%) fibrous PH lesions. The majority of segmental lesions in the TIP area were cellular, whereas all 21 segmental lesions in the PH area were fibrous. The segmental lesions in the NOS area were mixed cellular (33.1%) and fibrous (66.9%)



	NOS variant	PH variant	CEL variant	TIP variant	COL variant
TIP area	0	0	0	49	12
NOS area	35	3	28	26	36
PH area	0	18	0	0	3

Number of segmental lesion in each location; TIP, NOS, or PH area in each FSGS variant.

Fig. 5 Location heterogeneity of segmental lesions in each histological variant. Heterogeneity in terms of location was present of the segmental lesions. In the COL variant, segmental lesions were located in the TIP (12/51, 23.5%), NOS (36/51, 70.6%), and PH areas (3/51, 5.9%). In the TIP variant, segmental lesions were located in the TIP (49/75, 65.3%) and NOS areas (26/75, 34.7%), but not in the PH area. All segmental lesions in the CEL variant were located in the NOS area (28/28, 100%). Most of the segmental lesions in the PH variant were located in the PH area (18/21, 85.7%), with three located in the NOS area (3/21, 14.3%). All segmental lesions in the NOS variant were located in the NOS area (35/35, 100%). *Gray bars*, TIP area; *dashed bars*, NOS area; *dotted bars*, PH area



	NOS variant	PH variant	CEL variant	TIP variant	COL variant
Cellular	0	0	16	51	32
Fibrous	35	21	12	24	19

Number of segmental lesions with cellular or fibrousg subtype in each FSGS variant.

Fig. 6 Quality heterogeneity of segmental lesions in each histological variant. The quality composition, cellular (*white bars*) and fibrous (*black bars*) segmental lesions, in each variant is shown. Among the 210 segmental lesions, 99/210 (47.1%) were cellular and 111/210 (52.9%) were fibrous. In the COL variant, 32/51 (62.7%) were cellular and 19/51 (37.3%) were fibrous. The cellular subtype was also predominant in the TIP (51/75, 68%) and CEL variants (16/28, 57.1%). In contrast, all segmental lesions were fibrous in the NOS and PH variants. *Gray bars*, cellular; *black bars*, fibrous

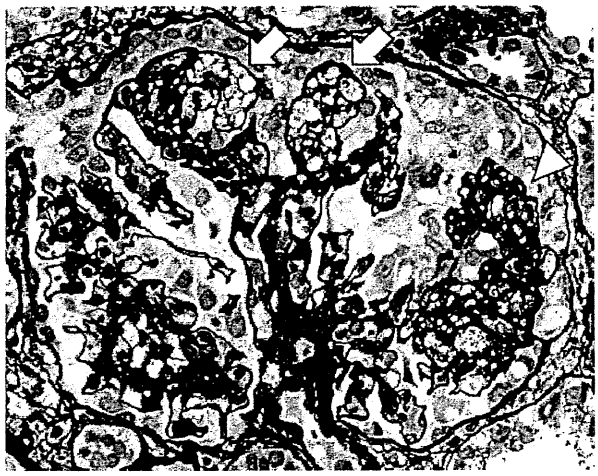


Fig. 7 Overlap of COL and CEL lesion histological findings. The glomerulus showed the coexistence of segmental tuft collapse (*arrow head*) and endocapillary hypercellularity with intracapillary foam cells (*arrow*). Overlap between the CEL lesion in the COL variant sometimes made it difficult to determine the variant. The CEL lesion was present in nine of 13 cases with COL variants in this study (silver methenamine stain, ×200)

predominantly TIP lesion location (10.4 ± 2.2 g/day), followed by the NOS location (4.6 ± 1.0 g/day), and the PH location (2.1 ± 0.4 g/day). Proteinuria was highest in the cellular subtype (11.8 ± 1.9 g/day), followed by the fibrocellular (3.4 ± 1.0 g/day), and fibrous subtypes (1.9 ± 0.3 g/day; Fig. 8b). The sCr level at final observation was highest for the

predominantly NOS location (4.0 ± 0.8 mg/dl) and was lower for the TIP location (1.4 ± 0.4 mg/dl) and PH location (1.2 ± 0.1 mg/dl), to a similar degree. However, the sCr level at the end of follow-up did not differ by the predominant quality factor: cellular, 3.2 ± 0.9 mg/dl; fibrocellular, 2.5 ± 0.9 mg/dl; and fibrous, 2.7 ± 0.7 mg/dl (Fig. 8c). No significant difference was evident in the other clinical parameters, including the sCr level at biopsy and proteinuria at final evaluation.

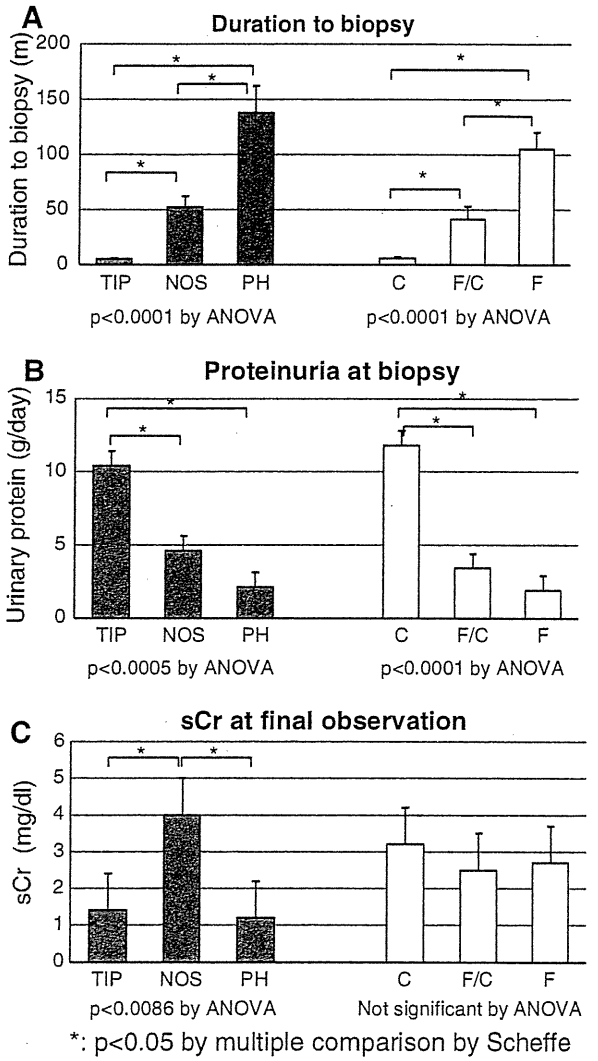


Fig. 8 Correlation between clinical parameters and dominant location/quality factors of segmental lesions. **a** Interval between onset and biopsy (months). **b** Urinary protein excretion at biopsy (g/day). **c** Serum creatinine (sCr) level at final observation (mg/dl). Both the location and quality of lesions were significantly correlated with disease duration and proteinuria at biopsy. The outcome, as reflected by the sCr at the end of follow-up, was significantly correlated with location, but not with quality of lesions

Dominant location/quality factors of segmental lesions correlation with histological parameters

Globally sclerotic glomeruli represented a significantly lower percentage of total glomeruli in the TIP location (4.2 ± 1.1%) compared with the NOS (22.6 ± 3.0%) and PH locations (19.0 ± 3.1%), and were lower in the cellular subtype (8.1 ± 2.7%) than in the fibrocellular (19.6 ± 3.4%) and fibrous subtypes (22.5 ± 3.2%; Fig. 9a). In contrast, the percentage of segmentally sclerotic glomeruli did not differ significantly among the location categories: TIP, 18.4 ± 2.3%; NOS, 20.3 ± 2.0%; and PH, 16.3 ± 1.9%. However, the percentage of segmentally sclerotic glomeruli was higher in the fibrocellular subtype (25.7 ± 2.6%) than in the cellular (17.2 ± 2.4%) and fibrous subtypes (17.0 ± 1.6%; Fig. 9b). The IF/TA score for the TIP category (0.91 ± 0.17) was significantly lower than the score for the NOS category (1.86 ± 0.13), which was not significantly different from the score for the PH category (1.53 ± 0.17). Additionally, the IF/TA score was lower for the cellular subtype (1.10 ± 0.15) compared with the fibrocellular (1.94 ± 0.22) and fibrous subtypes (1.67 ± 0.13; Fig. 9c).

Clinical relevance of the location and quality heterogeneity in each variant

To examine the clinical relevance of the location and quality heterogeneity, we examined the COL, TIP, and PH variants with different location categories (Supplemental Tables 2–4) and the COL, CEL, and TIP variants with different quality categories (Supplemental Tables 5–7). The results revealed that the location and quality heterogeneity of segmental lesions have some influence on the clinical and histological manifestations in each variant of FSGS, but further study with a greater number of patients is required to show distinct statistical differences.

Discussion

The present study indicated that location heterogeneity of glomerular segmental lesions was observed in the COL and TIP variants, and indistinctly in the PH variant. The CEL and NOS variants showed a homogenous location, because of their diagnostic

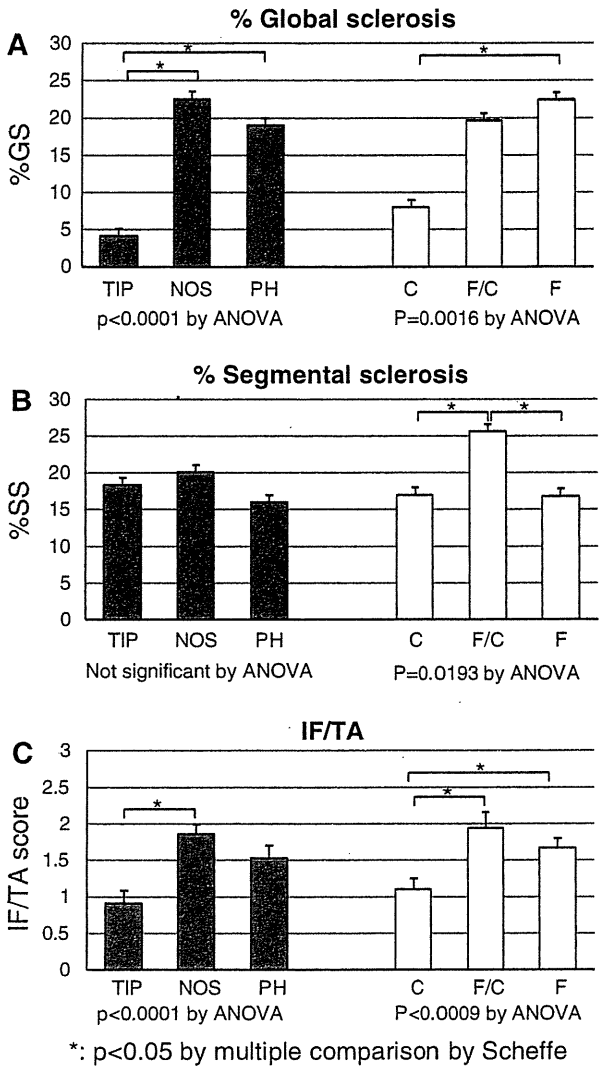


Fig. 9 Correlation between histological parameters and dominant location/quality factors of segmental lesions. **a** Globally sclerotic glomeruli as a percentage of the total number of glomeruli (%GS). **b** Segmentally sclerotic glomeruli as a percentage of the total number of glomeruli (%SS). **c** Score of interstitial fibrosis and tubular atrophy (IF/TA score). Both the location and quality of lesions were significantly correlated with %GS and the IF/TA score. Quality was correlated only weakly and location not at all with %SS, meaning that the percentage of segmentally sclerotic glomeruli was similar across location categories and quality subtypes

criteria. The clinical relevance of location heterogeneity was partly shown in the COL variant: a shorter duration to biopsy in the COL variants affecting the TIP area and a higher incidence of ESRD in the COL variants affecting the NOS area. The location factor for the segmental lesion may be important in assessing clinical and histological findings of the COL variants. The segmental COL lesion localized in the TIP or PH area may indicate less serious clinical manifestations than the typical COL variant, as reported previously [18–23]. In contrast, the clinical relevance of location heterogeneity was obscure in the TIP and PH variant, meaning that the detection of a single segmental lesion consistent with the TIP and PH variant is generally accepted as sufficient for determining variant classification.

Quality heterogeneity in terms of activity and chronicity of glomerular segmental lesions was also noticed in the COL, TIP, and CEL variants. The activity and chronicity of glomerular lesions are good indicators of the severity of various glomerular diseases [12–17]. Although histological activity and chronicity are controversial in FSGS, it is generally accepted that hypercellular lesions are frequently observed in patients with severe clinical manifestations, such as the COL or CEL variants of the Columbia classification. The present study also indicated that the cellular characteristics of segmental lesions were associated with a shorter delay to biopsy and severe proteinuria, and that the quality heterogeneity of segmental lesions reflected the different clinical and histological manifestations in the patients with COL and CEL variants.

Determining the dominant location and quality of glomerular segmental lesions may be useful for estimating clinical severity and for the histological classification of FSGS. The dominant location of lesions was significantly associated with several clinical and histological features, as originally suggested by D'Agati et al. [3]. Severe clinical manifestations and unfavorable outcomes were associated with the NOS location of segmental lesions, and a favorable outcome was associated with the TIP and PH locations, consistent with previous studies [5, 7, 17, 22]. The TIP location correlated well with severe proteinuria, shorter delay to biopsy, and favorable prognosis. The PH location was associated with the longest duration to biopsy, a lower level of proteinuria, and, similar to the TIP location, a favorable outcome. Similarly, the dominant quality factor (cellular, fibrocellular or fibrous) of lesions was significantly associated with the level of proteinuria at biopsy and the extent of glomerular sclerosis. The cellular subtype is associated with acute and severe clinical manifestation, and the fibrous subtype represents chronic and milder clinical presentation. Thus, the dominant quality as well as the dominant location

of glomerular segmental lesions is a good indicator of clinical manifestations.

The distinction between the COL and CEL variants requires further investigation due to their overlapping histological findings and the apparent histological heterogeneity of glomerular segmental lesions. Endocapillary hypercellularity, a diagnostic criterion of the CEL variant, can also be encountered in COL variant cases. Overlapping histological findings in the COL and CEL variants sometimes cause difficulty in identifying the variant [1]. This situation may be associated with the result that no significant difference in the clinical and histological findings was seen between the COL and CEL variants. Further studies are needed to identify distinct differences between the COL and CEL variants as applied to cases of histologically overlapping COL and CEL findings. Furthermore, it remains to be determined which histological findings, for example, epithelial hyperplasia or endocapillary proliferation, are, in fact, associated with disease activity and progression in FSGS.

In conclusion, histological heterogeneity of glomerular segmental lesions exists in all variants of the Columbia classification, except NOS, and reflects the clinical diversity within each variant of FSGS. Determining the dominant location and quality subtype of glomerular segmental lesions may be useful for classifying variants and estimating clinical severity and outcome in patients with FSGS. Although the generally conserved fidelity of location and dominance of histological features in the TIP, PH, and NOS variants support the utility of the Columbia classification, the COL and CEL variants warrant further investigation due to their overlapping histological findings and apparent histological heterogeneity of glomerular segmental lesions.

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特集 透析診療における分子バイオマーカーの新たな展開

[各論 — 日常透析診療に役立つ分子バイオマーカー]

Ⅸ 膠原病・血管炎

湯村 和子* 濱野 慶朋*

要旨 近年，高齢化社会になり，高齢者に好発する腎疾患からの透析導入患者が増えてきている．また，膠原病の腎障害のSLE腎炎からの透析患者の人数も減ることはない．透析導入後も，このような腎臓以外の多臓器障害を有する原疾患のコントロールが必要であり，バイオマーカーや臨床徴候をもとに，原疾患の再燃のキャッチを迅速に行い，治療を継続することが，生命維持には重要である．具体的には，急速進行性腎炎は，ANCA関連血管炎が多く，非特異的炎症徴候（発熱，体重減少，関節痛など），多臓器障害の出現増悪（肺病変など）やANCAの動向をみて，また，SLE腎炎でも，活動性の徴候（発熱，関節痛など）や血清補体価の動態で再燃をキャッチし，適切な治療を行わなければならない．

〈key point〉

Ⅰ．透析患者における膠原病・血管炎の実態

ここでの重要なポイント●

● 腎死で透析導入になっても，透析導入後もコントロールすべき原疾患があることを忘れないことが重要である．

1．膠 原 病

膠原病からの透析新規導入では，SLE腎炎（全身性エリテマトーデス；SLEの腎障害のループス腎炎と同義語，日本透析医学会統計調査委員会の統計の記載）からがもっとも多い．透析導入比率は全体の患者数の1％程度であり，年間大体300人前後である．関節リウマチからの透析導入は，二次性アミロイド腎症による．最近は関節リウマチの治療法が大きく進歩し，炎症のコントロールが容易になってきた．元来，

関節リウマチ
二次性アミロイド腎症

Key words 急速進行性腎炎，ANCA，SLE腎炎，血清補体価（CH50），CRP

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関節リウマチ患者数は，SLE より 10 倍程度多いのに，腎障害の患者数は少ない．

強皮症

一方，強皮症と腎臓との関連は，悪性高血圧による急性腎不全であり，透析診療での対応の場面はほとんどない．

2. 血管炎（急性進行性腎炎）

高齢化社会を迎え，高齢者に好発する急速進行性腎炎による透析導入患者は年々増加している．急速進行性腎炎は，単独に起こることもあり，腎限局性の血管炎として発熱などの全身症状もなく，他臓器の障害（間質性肺炎，多発性単神経炎，紫斑など）も伴わないこともある．多くは血管炎の一つの障害臓器として，高頻度に腎臓に急速進行性腎炎が起こる．高齢者の透析導入原疾患として注目すべき疾患である．

他臓器の障害を伴わないこともある

急速進行性腎炎は，顕微鏡的多発血管炎の主要徴候として出現する．本邦においては，MPO（ミエロペルオキシダーゼ）-ANCA（抗好中球細胞質抗体）が陽性の場合が多い．全身の臓器傷害としては，肺病変が多く，間質性肺炎から肺出血まで多岐にわたる．間質性肺炎は，腎障害出現以前より認められていることが多い．透析中の患者も，感染を契機に肺病変が増悪することがあり，注意しなければならない．他に高頻度の障害には，神経障害がある．多発性単神経炎が多いが，中枢性の場合もある．また，血管炎があれば，皮膚症状（紫斑）なども認める．

血管炎の多彩な徴候に関しては，BVAS（Birminghan vasculitis activity score）があるので参照されるとよい（日本語では，湯村和子 & BVAS で検索されると，いくつかの論文が抽出されるので参考にされるとよい）．

ここで述べる疾患で共通している点は，腎死で透析導入になっても，引き続きコントロールすべき原疾患があることを忘れてはいけないことである．

II. 透析患者における膠原病マーカーの読み方

ここでの重要なポイント

- 膠原病とくに，SLE 腎炎においては，病勢の安定性をキャッチするマーカーとして，血清補体価 CH50（補体成分 C3 もよい）が有用である．

1. SLE 腎炎

尿蛋白

副腎皮質ステロイド

長期に SLE 腎炎を加療しても，尿蛋白が陰性化しない場合は，透析導入を回避できないこともある．このような場合，少量の副腎皮質ステ

ロイド（以下，ステロイド薬と略す）が使用されている（頻度は高くないが，ステロイド薬を中止していることもある）．

CH50
C3

維持透析中であっても，血清補体価（CH50）（保険収載38点）やC3（保険収載70点）を測定することが重要である．抗核抗体（保険収載115点）は，SLE患者では，完全に陰性化する場合はまれで，活動性を鋭敏に反映することも少ない．もちろん，抗ds（double-standed）-DNA抗体（保険収載180点）も再燃時上昇するが，維持透析患者では実際的ではない．SLE活動性の基準としては尿異常は透析患者ではもちろん，ほかのSLE活動性基準にあげられる白血球や血小板減少などの検査所見も総合的に考慮し判断することが重要である．SLE腎炎の診断が付いていれば，疾患特異的マーカーとして，CH50などの補体系の変動で経過を見ていくと病勢を把握しやすい．

2. 関節リウマチ

関節リウマチが原疾患で透析導入となる例は少ないが，維持透析中に関節リウマチを疑う場合は皆無ではない．まず，関節リウマチを疑ったら

RF

RF（rheumatoid factor）（保険収載30点）を調べることが通常である．比較的陽性率が高く，米国リウマチ学会の診断基準（**表**）[1]の唯一の血清マーカーになっている．

抗CCP抗体

その他のマーカーとしては，抗CCP（環状シトルリンペプチド；シトルリン）抗体は簡易に検出できるシトルリン化器質が開発され，近年保険収載され（保険点数210点），関節リウマチに特異度が高く診断のバ

表　関節リウマチ（RA）の分類基準（米国リウマチ学会，1987年）

① 朝のこわばり；最大の改善をみるまでに，1時間以上かかる
② 同時に，3領域以上（下記14関節のうち）の関節炎 左右のPIP，MCP，手，肘，膝，足，MTPで計14
③ 手，PIP，MCPの少なくとも1領域の関節炎
④ 対称性の関節炎；②で定義した領域において
⑤ リウマトイド結節
⑥ 血清リウマトイド因子陽性
⑦ X線上，手/指関節の骨びらん，近傍の骨萎縮
・1から4は6週間以上持続し，関節炎とは腫脹または液貯留があるものをいう ・7項目中4項目以上満たす疾患をRAと分類する
PIP：近位指節間関節，MCP：中手指節間関節，MTP：中足趾節間関節 手，足とは手首（wrist），足首（ankle）のことである（上記の14関節は，RAでの罹患分布を列挙したのでなく，感度，特異度を高める項目を選んだものである）．

〔Arnett, F. C., et al.：Arthritis Rheum.　1988；31：315-324[1]より引用〕

MMP-3

イオマーカーとして注目されている．また，MMP-3（matrix metalloproteinase-3）（保険収載 120 点）は，滑膜表層細胞で産生される軟骨のプロテオグリカンを分解する酵素で，血清 MMP-3 高値は，増殖性骨炎を意味する．MMP-3 は，関節リウマチの診断の感度は高いが，特異度は低い．

感度としては MMP-3＞RF＞抗 CCP 抗体の順に高い．特異度は抗 CCP 抗体で高く，抗 CCP 抗体陰性の場合は関節リウマチとは言えない．RF/抗 CCP 抗体が＋/＋であれば，80 %が関節リウマチと診断できる．このことは，データはないが透析患者での診断も同じと考えてよい．

III. 透析患者における血管炎マーカーの読み方

ここでの重要なポイント

- 血管炎，とくに急速進行性腎炎からの透析導入患者の再燃などのキャッチには，血管炎マーカーの ANCA の測定が有用であるが，CRP 陽性も参考にするとよい．

ステロイド薬などの免疫抑制療法によっても腎機能が改善せず，透析導入時，ANCA が陽性である場合，ステロイド薬などの減量のためのマーカーとして ANCA をチェックすることが多い．透析導入時は，C 反応性蛋白（CRP）は陰性化している症例がほとんどである．

病勢が落ち着くと ANCA も陰性化する．ステロイド薬などの減量・中止の症例では，血痰，紫斑，関節痛，発熱などの血管炎を疑う症状が出現し，再燃することも多い．このような場合，CRP 陽性を伴い，

ワンポイント アドバイス

SLE 患者が，透析導入後もステロイド薬を使用する場合がありますが，どんなことに注意したらよいでしょうか？

膠原病，血管炎など，原疾患のコントロールのために，ステロイド薬が透析導入後も使用されている場合が多い．ステロイド薬使用による易感染性に注意する．ステロイド薬によって糖尿病が誘発された場合は，より注意が必要である．また，原疾患の腎以外の再燃（腎臓は burn out しても全身の活動性は残されている）には注意し，ここで述べたいずれの疾患の場合も，ステロイド薬増量があることを知っておかなければならない．もちろん，病勢が治まっている場合は，減量を試みる．ステロイド薬をむやみに中止すると，再燃の発見が遅れることもある（原疾患を忘れがちである）．漫然と高用量のステロイド薬を使用することは避けなければならないが，少量のステロイド薬は，長期にわたり使用した場合は（ループス腎炎などは 20～30 年ステロイド薬を使用している場合もある），安易な中止は副腎不全をきたすこともありうるので，むしろ避けるべきである．

ANCAも上昇する場合が多い．

〈抗好中球細胞質抗体（anti-neutrophil cytoplasmic autoantibody；ANCA）〉

病理学的に壊死性半月体形成性腎炎を示し急速進行性腎炎を呈する血管炎では，この自己抗体が産生される．大きく分けて，myeloperoxiase（MPO）-ANCA（保険収載290点）とproteinase-3（PR3）-ANCA（保険収載290点）に分けられる．本邦に多いANCA関連血管炎は，顕微鏡的多発動脈炎によることが多く，MPO-ANCA陽性である．PR3-ANCAはWegener肉芽腫症で陽性になることが多いといわれている．

MPO-ANCA
PR3-ANCA

測定方法は，歴史的には間接蛍光抗体法で発見された経緯がある．蛍光染色パターン分類は，cytoplasmic（C）-ANCA（好中球細胞質がびまん性顆粒状に染色される）とperinuclear（P）-ANCA（各周辺の細胞質が強く染色される）二つのタイプに分けられる．保険適応の検査となっている（保険点数290点）．また，定量的には，酵素抗体法（ELISA）で測定する．MPOが対応抗原であるMPO-ANCA（正常値20 EU未満，ニプロ社製測定試薬）とPR3に対する抗原のPR3-ANCA（正常値10 EU以下，ES社測定試薬）に分けられる．これらも保険適応になっている．日常的には，透析患者でも，ELISA法で定量測定することが望ましい．

ELISA

Ⅳ．透析患者におけるC反応性蛋白（CRP）の読み方

ここでの重要なポイント●

● 基礎疾患に膠原病や血管炎があると，CRPの陽性陰性の判断が異なる．

CRP（詳細はp.29「感染症」の項参照）は，急性期炎症とくに感染症のマーカーとして有名である．基礎疾患に膠原病や血管炎があると，CRPの陽性陰性の判断の仕方が異なる．つまり，透析患者であるか否かにかかわらず，SLE患者にSLEとしての活動性があり発熱があっても，CRPは陰性である．SLE患者でのCRP上昇の発熱は，まず感染を考えなければならない．

CRP陽性陰性の判断

感染

一方，血管炎患者で，CRP上昇の判断は困難なことが多い．CRP上昇が血管炎としての非特異的炎症反応なのか，感染を伴っているかの判断が重要である．血管炎の発症・再燃の契機には感染との関連が密である場合が多い．CRP陽性の場合，まずは一般的感染症の対処を行うことが多い．数日で解熱など改善しない場合は，CRPと同時にオーダーしたANCAのデータをみて，血管炎の再燃かを判断する．

おわりに

SLE腎炎と透析時の注意点など詳細に記述した論文はない．諸外国ではSLE腎炎の患者が腎移植を受け，本邦のように維持透析を受けることが少ないからでもある．適切な論文はないが，SLE腎炎患者が維持透析を受ける場合は，SLEの活動性が高くなる（再燃：白血球減少，血小板減少，低補体血症，抗ds-DNA抗体上昇，徴候として関節痛，CRP陰性の発熱，紅斑の出現）こともあり，ここで述べたバイオマーカーは再燃を疑ったらチェックすることが肝要である[2]．

ここで述べた疾患群は，まれな疾患ではあるが，原疾患が何かを念頭に透析医療を行わなくてはいけない．数少ないが有用なバイオマーカーがあり，熟知することが重要である．

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Summary

Biomarker of SLE nephritis and ANCA associated vasculitis

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In recent years, the number of patients initially receiving dialysis and those having kidney disease who are senior citizens, has gradually increased. The number of people receiving dialysis due to SLE nephritis does not seem to have decreased. Control of diseases related to SLE is required after dialysis introduction. Diseases leading to multiple organ failure as well as kidney dysfunction may be recognized by examining biomarkers and other clinical indications which are important in indicating the presence of recurring diseases quickly and providing life time maintenance therapy. ANCA associated vasculitis specifically indicates elevated ANCA in many recurrent cases. We must recognize recurrent disease conditions when delivering hemodialysis. Cases exhibiting active signs and changes in serum complement (CH50) titres must be treated appropriately.

Key words : rapidly progressive glomerulonephritis, ANCA (anti-neutrophil cytoplasmic autoantibody), SLE nephritis, serum complement 50, C-reactive protein

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Concise report

Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK

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Abstract

Objectives. The epidemiological manifestations of ANCA-associated vasculitis (AAV) differ geographically. However, there have been no prospective studies comparing the incidence of AAV between Japan and Europe over the same time period using the same case definitions.

Methods. The incidence of AAV was determined by a population-based method in Miyazaki prefecture, Japan, and Norfolk, UK, between 2005 and 2009. Patients with AAV were defined and classified according to the European Medicines Agency (EMEA) algorithm.

Results. The number of incident cases of AAV in Japan and the UK were 86 and 50, respectively, and the average annual incidence over the 5-year period was 22.6/million (95% CI 19.1, 26.2) and 21.8/million (95% CI 12.6, 30.9) in Japan and the UK, respectively. The average age was higher in patients in Japan than in patients in the UK [mean (median), 69.7 (72) *vs* 60.5 (61) years]. Microscopic polyangiitis (MPA) was the predominant subtype in Japan (83%), while granulomatosis with polyangiitis (Wegener's) was more frequent in the UK (66%). As for the pattern of ANCA positivity, >80% of Japanese patients were pANCA/MPO positive, whereas two-thirds of UK patients were cANCA/PR3 positive. Renal involvement in MPA was very common in both countries, but was much less common in granulomatosis with polyangiitis in Japan compared with the UK.

Conclusion. There was no major difference in AAV incidence between Japan and the UK, but this prospective study found MPA and MPO-ANCA to be more common in Japan and granulomatosis with polyangiitis and PR3-ANCA to be more common in the UK, in line with earlier reports.

Key words: Microscopic polyangiitis, Granulomatosis with polyangiitis (Wegener's), Churg–Strauss syndrome, Myeloperoxidase anti-neutrophil cytoplasmic antibody, Proteinase 3 anti-neutrophil cytoplasmic antibody, Incidence, Epidemiological study.

SCIENCE

Introduction

Geographical differences in the epidemiology of the vasculitides have been observed. Takayasu arteritis and Kawasaki arteritis are more common, but GCA is less common in Japan compared with European and/or North American countries. As for ANCA-associated vasculitis (AAV), the incidence of granulomatosis with polyangiitis (Wegener's) is higher than that of microscopic polyangiitis (MPA) in northern Europe [1–3]. On the other hand, MPA is predominant among cases of AAV in southern Europe [4]. However, some recent papers have indicated that the incidence of MPA cannot be correlated with latitude [5, 6]. In Japan, the prevalence of MPA and/or renal limited

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vasculitis (RLV) has been reported to be much higher than granulomatosis with polyangiitis by a hospital-based nationwide survey [7]. However, there have been no studies investigating the incidence, rather than the prevalence, of AAV in Japan and comparing the clinical features of AAV between Japan and Europe or the USA up to the year 2005.

To elucidate the potential differences in the incidence and clinical phenotype of new-onset AAV, an international collaboration study was started in 2004. In 2005, before the epidemiology study in Japan, UK members visited Miyazaki prefecture to inspect the medical facilities and survey the population and advised Japanese members to conduct a population-based survey of AAV. The first study was performed as a retrospective study in renal units in Miyazaki prefecture from 2000 to 2004 and revealed that the estimated annual incidence of primary renal vasculitis was 14.8/million [8]. Watts *et al.* [9] compared the incidence of renal vasculitis prospectively determined in Norfolk, UK, with Miyazaki, Japan, and reported that the overall occurrence of renal vasculitis was similar between the two countries, but the clinical phenotypes were very different, with MPA predominating in Japan and granulomatosis with polyangiitis predominating in the UK.

Epidemiological studies on potential differences of AAV in the world are useful to investigate the aetiology and pathogenesis as well as to inform genetic and therapeutic studies of AAV. This study was planned to clarify the epidemiological differences between Japanese and European patients with AAV.

Subjects and methods

Japanese population

This study was done between 1 January 2005 and 31 December 2009 in five renal, three rheumatology and two otolaryngology units, which are the only referral centres for new-onset cases of AAV [MPA, granulomatosis with polyangiitis and Churg–Strauss syndrome (CSS)] in the western, southern and central area of Miyazaki prefecture. Each unit prospectively registered new-onset cases of AAV, and one investigator (S.F.) collected and reviewed the data from all centres each year. The population in these areas seldom undergoes medical examinations in the other prefectures. The populations of adults (aged >15 years) and seniors (>65 years old) in these areas comprised 759 000 (male, 47.5%) and 220 000 persons, respectively, in 2009. The study population was relatively static and we estimated the total immigration rate out of the study area during 2005–2009 to be <2%. The study obtained ethical approval in each country (Ethical committees of the University of Miyazaki Hospital, Miyazaki, Japan, and University of East Anglia, Norwich, UK).

UK population

Since 1988 the Norfolk and Norwich University Hospital (NNUH) has maintained a prospective register of its patients with AAV, as previously reported [10]. This institution is the single, central referral centre for a stable and ethnically homogeneous population of ~500 000. The study area covers a geographically isolated coastal region in eastern England, allowing the population to be well defined and therefore suitable for epidemiological studies over a prolonged period of time. The estimated 2009 population was 459 000 (males 48.1%). Around 20.9% of the population is aged >65 years, which is higher than the average for England generally (15.9%) (Office for National Statistics, www.statistics.gov/).

Classification of vasculitis

Patients with AAV were defined and classified according to the European Medicines Agency (EMEA) algorithm [10]. This uses an algorithm to classify vasculitis and utilizes the American College of Rheumatology (ACR) criteria (1990) and the Chapel Hill Consensus Conference definitions. Using this approach, RLV is placed within MPA.

Determination of ANCA specificities

ANCA was determined by IIF and by ELISA for PR3/MPO specificity using commercially available kits. A comparative study of the ELISA kits used in Europe and Japan demonstrated close correlations in specificity and sensitivity [11].

Statistical analysis

Continuous data were presented as the means (S.D.). Annual incidences were presented as simple proportions with 95% CIs, and calculated using the Poisson distribution. Comparisons between the Japan and UK studies were made using the chi-square test for dichotomized variables and unpaired *t*-test for continuous variables. Values of $P < 0.05$ were considered statistically significant.

Results

Table 1 shows the incidence, clinical phenotype and ANCA subtypes of AAV in Japan and the UK. In Japan, the numbers of incident AAV were 14, 21, 18, 19 and 14 in the years 2005, 2006, 2007, 2008 and 2009, respectively. The average annual incidence of AAV over the 5-year period was 22.6/million adults (95% CI 19.1, 26.2). On the other hand, in the UK, the numbers were 14, 5, 11, 15 and 5 in each year, and the annual incidence per million adults was 21.8 (95% C.I. 12.6, 30.9). The male-to-female ratios were identical in Japan and the UK, but the average age was significantly higher in Japan compared with the UK [69.7 (11.0) *vs* 60.5 (14.8) years, $P < 0.001$), and the difference in the median age was ~10 years. However, the mean ages in the patients with MPA or granulomatosis with polyangiitis were not different between the two countries [MPA, Japan ($n = 69$) *vs* UK ($n = 15$), 71.6 (10.0) *vs* 68.7 (13.3) years, $P = 0.333$; granulomatosis with polyangiitis, Japan ($n = 8$) *vs* UK ($n = 33$), 61.4 (9.9) *vs* 56.9 (15.2) years, $P = 0.440$]. As for seniors, the annual incidence was 57.0/million and 47.9/million in Japan and the UK, respectively. In both areas, the annual incidence of MPA was about 10 times higher in seniors compared with younger adults (from 15 to 64 years old). Among patients with AAV, MPA was the predominant type in Japan [annual incidence 18.2 (95% CI

Table 1 Comparison of the disease spectrum and ANCA status of AAV between Japan and the UK

Disease spectrum and ANCA status	Japan	UK
Numbers of total AAV	86	50
Male *vs* female	42 *vs* 44	24 *vs* 26
Mean (median) age, years	69.7 (72)*	60.5 (61)
pANCA/MPO, *n* (%)	72 (84)**	15 (30)
cANCA/PR3, *n* (%)	6 (7)**	29 (58)
Negative, *n* (%)	8 (9)	6 (12)
Annual incidence/million		
Adults		
Total AAV	22.6 (19.1, 26.2)	21.8 (12.6, 30.9)
MPA	18.2 (14.3, 22.0)	6.5 (1.9, 11.2)
Granulomatosis with polyangiitis	2.1 (0.6, 3.7)	14.3 (5.8, 23.0)
CSS	2.4 (0.3, 4.4)	0.9 (0, 1.9)
Seniors		
Total AAV	57.0 (53.4, 60.6)	47.9 (25.0, 70.8)
MPA	50.7 (38.3, 63.0)	20.8 (−0.6, 42.2)
Granulomatosis with polyangiitis	2.7 (−0.8, 6.3)	25.0 (14.6, 35.4)

95% CI values are given within parentheses for annual incidence values. *$P < 0.001$ by unpaired *t*-test; **$P < 0.001$ by chi-square test.

Table 2 Comparison of the organ involvements of new-onset AAV between Japan and the UK

Organ involvement	Japan	UK	*P*-value
Numbers of total AAV	86	50	
ENT	13 (15)	32 (64)	<0.001
Respiratory	37 (43)	39 (78)	<0.001
Nervous	15 (17)	9 (18)	0.934
Gastrointestinal	4 (5)	7 (14)	0.098
Renal	69 (80)	45 (90)	0.155
MPA	69	15	
ENT	5 (7)	3 (20)	0.148
Respiratory	25 (36)	9 (60)	0.145
Renal	64 (93)	15 (100)	0.580
Granulomatosis with polyangiitis	8	33	
ENT	8 (100)	28 (85)	0.576
Respiratory	3 (38)	28 (85)	<0.05
Renal	3 (38)	30 (90)	<0.01

Data are expressed as *n* (%) unless otherwise specified.

14.3, 22.0)], while granulomatosis with polyangiitis was predominant in the UK [annual incidence 14.3 (95% CI 5.8, 23.0)]. There were also significant differences in the pattern of ANCA positivity. More than 80% of Japanese patients were pANCA/MPO positive, whereas two-thirds of UK patients were cANCA/PR3 positive.

Table 2 shows the comparison of clinical features between the two countries. ENT and respiratory involvements were more common in the UK compared with Japan. Renal involvement in MPA was very common in both countries, but was much less common in granulomatosis with polyangiitis in Japan compared with the UK. Respiratory involvement in granulomatosis with polyangiitis was also less common in Japan than the UK.

Discussion

A geographical difference in the incidence of AAV has been suggested [1–4]. We previously reported that the clinical phenotype and ANCA specificities of primary renal vasculitis were quite different between Japan and the UK [8, 9]. Previously there were no cases of granulomatosis with polyangiitis/PR3-ANCA detected in Miyazaki, now there have been six cases of granulomatosis with polyangiitis and eight cases of PR3-ANCA diagnosed in Japan. The previous retrospective survey was conducted only in the renal units, whereas the present prospective study was performed in rheumatology and otolaryngology units that are the referral centres for the cases of AAV (with or without renal involvement) in addition to renal units. This may be the reason behind the discrepancy between the two studies. The present prospective study revealed for the first time that the incidence of AAV was similar between Japan and the UK, but MPA was predominant in Japan, whereas granulomatosis with polyangiitis was more common in the UK among patients with AAV. The characteristics of the profiles of patients with AAV in Miyazaki, Japan, were as follows: (i) 80% had MPA, (ii) 84% were pANCA/MPO positive, (iii) the mean and median ages (70 and 72 years) were high and (iv) renal and respiratory involvements in granulomatosis with polyangiitis were less common.

Latitude may affect geographical differences in the incidence of AAV. European studies have shown that granulomatosis with polyangiitis is more common in high-latitude areas than low-latitude areas. For example,

the incidences of granulomatosis with polyangiitis and MPA are 10.5 and 2.7/million, respectively, in Tromsø, Norway (latitude 70° north) [12], 7.9 and 2.7/million, respectively, in Schleswig-Holstein, Germany (latitude 51° north) [3] and 3.0 and 7.9/million, respectively, in Lugo, Spain (latitude 43° north) [4]. There have been no reports regarding the incidence of granulomatosis with polyangiitis in areas more southern than latitude 40° north, but the latitude of Miyazaki prefecture, which is on Kyushu, the southernmost of the four major islands of Japan, is almost 30° north. The incidence of granulomatosis with polyangiitis has not yet been clarified in other areas in Japan, but data from our 1998 nationwide survey showed that the annual prevalence of patients with granulomatosis with polyangiitis was very low compared with that of MPA (granulomatosis with polyangiitis 2.3/million and MPA 13.8/million) [7]. Environmental factors and very different triggers at different latitudes may affect the occurrence of different clinical phenotypes. On the other hand, Gatenby *et al.* [5] recently described an inverse association between latitude [low regional ambient ultraviolet (UV) radiation] and the incidence of granulomatosis with polyangiitis, but not MPA. Vitamin D levels are low at high latitudes; polymorphisms in vitamin D receptor-binding genes are common in individuals of European and Asian descent, and this may explain the distribution of multiple sclerosis and other autoimmune diseases, which tend to occur with increased frequency at higher latitudes [13].

Race differences and/or genetic backgrounds might also contribute to the proportions of the AAV and/or ANCA subtypes. In a US cohort study, Caucasians comprised > 90% of all granulomatosis with polyangiitis patients, whereas African Americans, Hispanics and Asians together represented only 1–4% of patients [14]. The population in the European studies consisted exclusively of Caucasians [1–3, 12]. On the other hand, in a study of 426 patients from China, 20% were classified as having granulomatosis with polyangiitis and 80% as having MPA, and only 16% were cANCA/PR3 positive [15]. Among Japanese patients with MPA and/or RLV, 79–93% are positive for MPO-ANCA [7], compared with 44–69% of European patients [4, 16]. Genetic differences between the two populations may explain the observed differences. For example, European population substructure studies have shown that people from northern and southern Europe have different genetic backgrounds [17]. Our previous multicentre collaborative study demonstrated that HLA-DR0901 is much more prevalent among MPA/MPO-ANCA-positive patients than in healthy controls [18]. Another example is RA, which occurs in both Europe and Japan, but with a different genetic background: PTNP22 polymorphism is strongly associated with RA in Europe, but the PTNP22 polymorphism does not occur in the Japanese population [19]. However, appropriate international studies using standardized methods of classification and genetic profiling have not been performed. For this reason, the results of recent joint studies undertaken by the European Vasculitis Study Group (EUVAS), the ACR and the Japanese government in order to define new classifications and diagnosis criteria are greatly anticipated [20].

The average age of patients with AAV was significantly higher in Japan compared with the UK, whereas the average age of patients with MPA or granulomatosis with polyangiitis was not different. The annual incidence of MPA was about 10 times higher in seniors compared with young adults in both countries. Considering these findings, we think that the reason for a substantial difference in the mean age between the two countries is due to the large number of patients with MPA in Japan.

MPA patients without renal involvement were much less common in both countries. On the other hand, in the UK, granulomatosis with polyangiitis was more common, and the majority of these patients had ENT, respiratory and renal involvement. In the previous retrospective epidemiological study of primary renal vasculitis performed in Miyazaki prefecture in 2000–2004, no renal vasculitis patients with granulomatosis with polyangiitis were seen [8]. Only three granulomatosis with polyangiitis patients with renal involvement were found in the present study from 2005 to 2009. Taken together, the results from the 10-year span of these studies suggest that renal involvement in granulomatosis with polyangiitis may be much less common in Japan than in the UK.

The incidence of CSS has fallen dramatically in the UK compared with earlier reports from the Norfolk area [2]. We do not think it is due to a change in classification, as we have carefully reclassified all our patients according to the EMEA algorithm [10]. It could be due to a change in environmental factors, but we do not know which ones, or due to the treatment of asthma with newer drugs, making it less likely that the patient will develop CSS.

In conclusion, the clinical features and ANCA specificities of AAV were quite different between Japan and the UK. To clarify whether the different aetiologies and genetic backgrounds may affect the occurrence of different clinical phenotypes in various populations, international collaboration studies using the same methodology will be needed.

Rheumatology key messages

- The incidence of AAV did not differ between Japan and the UK.
- MPA was the predominant subtype in Japan, while granulomatosis with polyangiitis was predominant in the UK.
- The serum MPO/PR3-ANCA ratio in AAV patients was much higher in Japan than the UK.

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