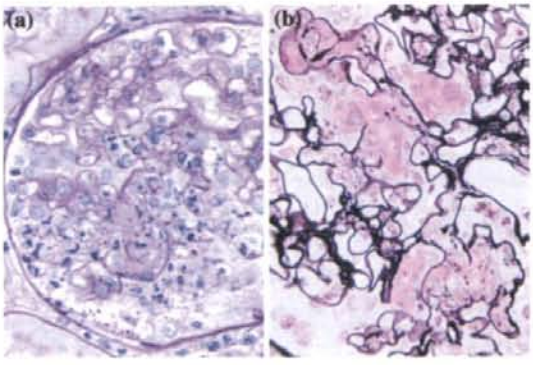


Fig. 1 Early stage of MPO-ANCA-related glomerulonephritis. Neutrophilic infiltration into the glomerular capillary lumen can be seen (**a**), followed by microthrombosis before disruption of the glomerular capillary wall (**b**). (**a** PAS stain, (**b**) PAM stain)

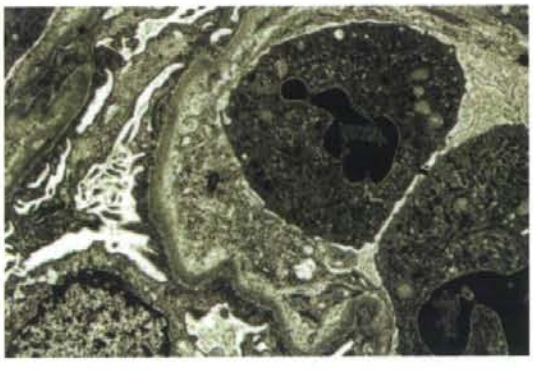


Fig. 2 Electron-microscopy findings of MPO-ANCA-related glomerulonephritis. Degranulated neutrophils are present with marked subendothelial edema due to endothelial injury. (Double-stained with uranyl acetate and lead citrate. ×10,000)

lesion is present at the end stage of crescentic glomerulonephritis, from which ischemic or obsolescent glomeruli should be excluded (Fig. 9). Segmental sclerosis is defined as a sclerosed area of scarring involving less than 50% of the glomerulus [17].

Tubulointerstitium

ANCA-related vasculitis sometimes involves interstitial inflammation, which is known as peritubular capillaritis. This lesion is defined by the presence of inflammatory cells within the capillary lumina, which often adhere to the capillary wall. Inflammatory cells consist mainly of neutrophils mingled with lymphocytes and plasma cells

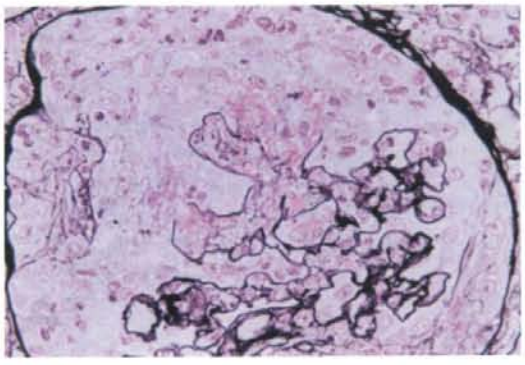


Fig. 3 Glomerular tuft necrosis. Destruction of the glomerular basement membrane induces cellular crescent formation in which fibrin is present inside and outside of the GBM (PAM stain)

(Fig. 10). Even when glomerular lesions are not remarkable, prominent tubulointerstitial inflammation can be seen in association with an impairment of renal function. Tubulointerstitial lesions are composed of interstitial inflammation, tubulitis, destruction of the tubular basement membrane (TBM), peritubular capillaritis, phlebitis, and granulomatous lesion. These lesions present as an acute and active process, whereas interstitial fibrosis and tubular atrophy are chronic lesions.

Interstitial inflammation

Interstitial inflammation is defined as an excess of inflammatory cells within the cortical interstitium, excluding the subcapsular area and the area of surrounding global glomerulosclerosis [7]. Accumulation of polymorphs as well as mononuclear cells in the peritubular capillary associated with the disruption of the capillary wall is defined as peritubular capillaritis, which is often combined with extravasation of erythrocytes [19].

Tubulitis and destruction of the TBM

According to the Banff 97 classification [19], grades of tubulitis ("t" score) are based on the greatest number of infiltrating mononuclear cells in the tubular epithelium (that is, having breached the TBM and lying beneath or between tubular cells) per tubular cross-section; if the tubule is sectioned longitudinally, the results are expressed per ten tubular cells (the average number of cells per cross-section). EUVAS scoring uses the term "intra-epithelial infiltrate" instead of "tubulitis" [7]. Inflammatory tubular injury, destruction of tubular basement membranes, and/or acute tubular necrosis is included as significant histologic findings in the "t3" grade [19]. In the case of ANCA-

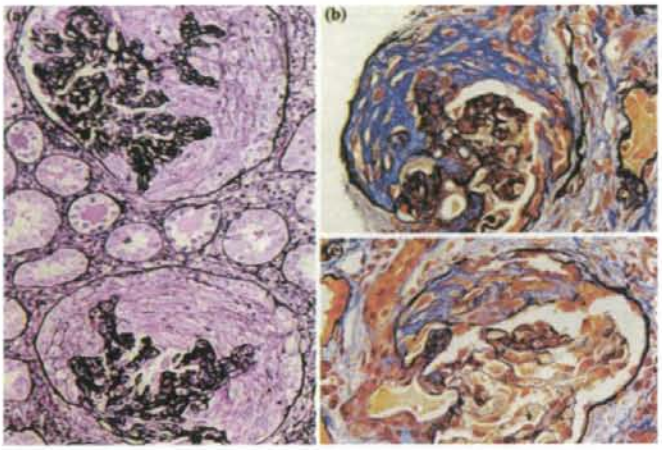


Fig. 4 Glomerular crescent. Cellular crescent = more than 50% of the crescent occupied by cells (**a**) (PAM stain). Fibrous crescent = more than 90% of the crescent occupied by extracellular matrix (**b**) (PAM-Masson stain). Fibrocellular crescent = less than 50% of the crescent occupied by the cells and less than 90% of the crescent occupied by extracellular matrix (**c**) (PAM-Masson stain)

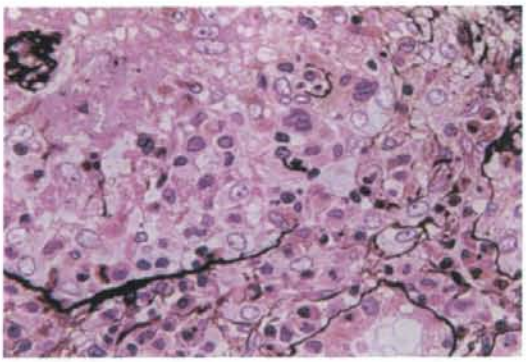


Fig. 5 Destruction of the basement membrane of Bowman's capsule. Infiltrating lymphocytic cells, plasma cells, and macrophages surround the lesion (PAM stain)

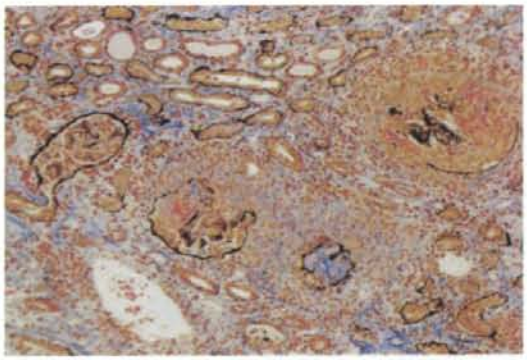


Fig. 7 Granulomatous reaction with destruction of Bowman's capsule. Accumulation of epitheloid cells is seen around a disrupted Bowman's capsule and sclerotic glomerulus (PAM-Masson stain)

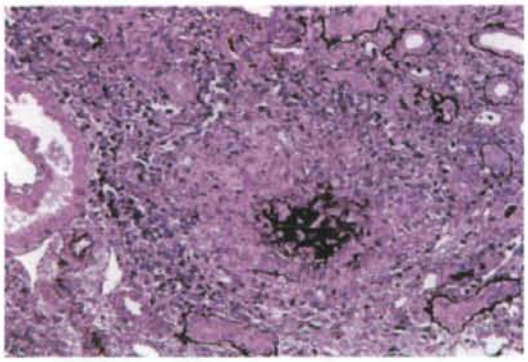


Fig. 6 Destruction of Bowman's capsule around a sclerotic glomerulus. Periglomerular granulomatous dense infiltrate is seen around a sclerotic glomerulus with destruction of Bowman's capsule (PAM stain)

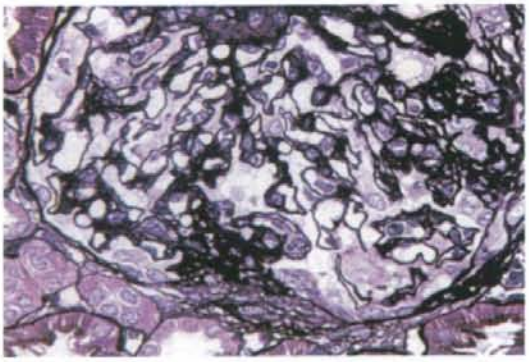


Fig. 8 Adhesion/synechia. A lesion with a local area of fibrous continuity between the glomerular tuft and Bowman's capsule is seen without extracapillary proliferation (PAM stain)

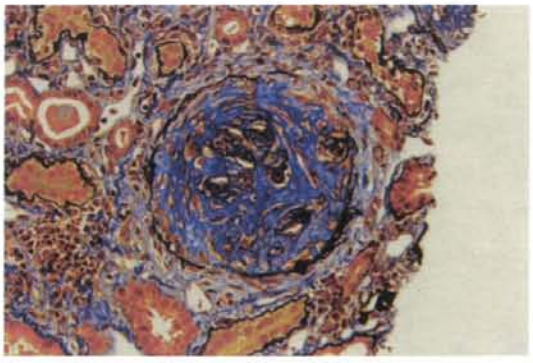


Fig. 9 Global sclerosis of the glomerulus of ANCA-related vasculitis. Bowman's space is occupied by a proliferation of collagen fiber mingled with epithelial cells. The basement membrane of Bowman's capsule is disrupted, inducing a periglomerular fibrosis (PAM-Masson stain)

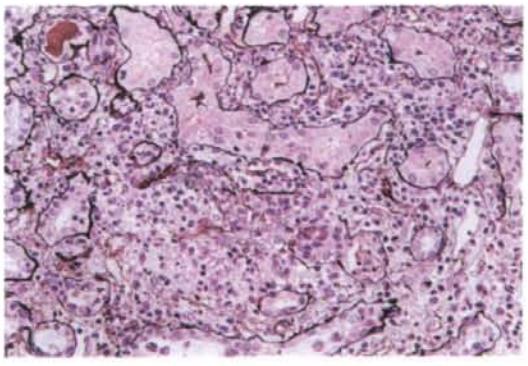


Fig. 11 Disruption of the tubular basement membrane induces a granulomatous reaction in MPO-ANCA-related interstitial inflammation (PAM stain)

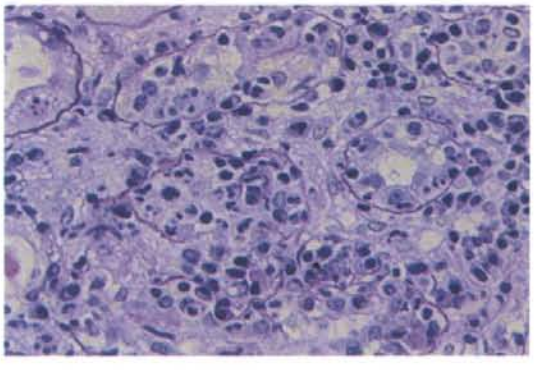


Fig. 10 ANCA-related tubulointerstitial nephritis. Early phase of ANCA-related peritubular capillaritis may involve a tubulointerstitial lesion, which consists of neutrophils mingled with lymphocytes and plasma cells (PAS stain)

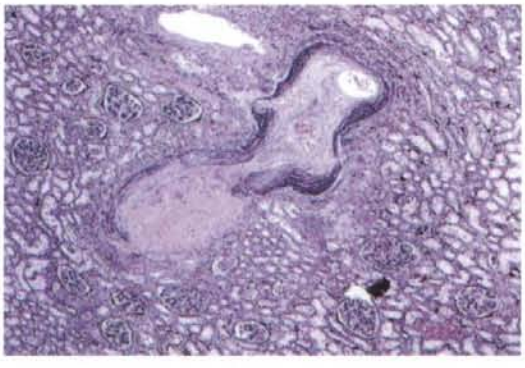


Fig. 12 MPO-ANCA-positive polyarteritis nodosa. Arcuate artery shows necrotizing arteritis without glomerular involvement (PAM stain)

related interstitial inflammation in Japan, almost all of the cases can be graded as "t3" because destruction of the TBM is usually present (Fig. 11). An interstitial granulomatous lesion can be seen together with destruction of the basement membrane of Bowman's capsule or TBM (Figs. 6, 7, 11).

Interstitial fibrosis and tubular atrophy

Tubular atrophy is defined by a thick irregular TBM with decreased diameter of the tubules. It is scored according to the percent of the cortical area involved, excluding the subcapsular area. Interstitial fibrosis is defined as increased

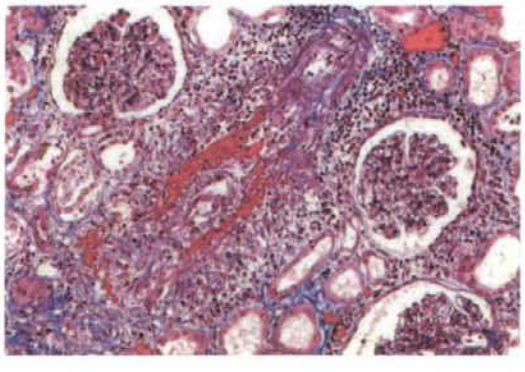


Fig. 13 Fibrinoid necrosis in a small artery in an MPO-ANCA-positive patient (Masson stain)

extracellular matrix separating tubules in the cortical area, excluding the subcapsular area [7].

Vascular system

Vasculitis is defined by the presence of leukocytic inflammation in the vessel wall with reactive damage to mural structures [2, 20]. Vasculitis is usually found in the kidney, as well as in the systemic organs, including the lung, bronchus, nasal cavity, gastrointestinal tract, skin, nerve, and muscles in ANCA-positive patients. Standardized names and definitions of primary systemic vasculitis have been adopted from the Nomenclature of Systemic Vasculitis in the Chapel Hill Consensus Conference (CHCC) [2]. In this categorization made according to the size of the artery, large vessel vasculitis, medium-sized vessel vasculitis, and small vessel vasculitis were classified. Large vessel refers to the aorta and the largest branches directed toward major body regions; medium-sized vessel refers to the area from the main visceral arteries (e.g., renal, hepatic, coronary, and mesenteric arteries) to the distal arterial radicals that connect with arterioles. The vasculature of the kidney is composed of medium-sized arteries (renal artery, interlobar artery, arcuate artery, interlobular artery) and small vessels, including small-sized arteries (afferent arteriole, efferent arteriole), capillaries (glomerular capillary and peritubular capillary), and venules. ANCA-related vasculitis, such as WG, MPA, and CSS, typically affects small-vessel vasculitis, which shows histologically fibrinoid necrosis in the vessel wall [1]. By contrast, polyarteritis nodosa (PN), which is usually ANCA negative, is designated as vasculitis of medium-sized or small arteries without vasculitis in the glomerular capillaries and venules. However, some Japanese patients may also display MPO-ANCA (ANCA directed against myeloperoxidase as determined by ELISA), which reveals necrotizing vasculitis in medium-sized arteries without glomerular involvement (Fig. 12).

Fibrinoid necrosis

Necrotizing vasculitis showing fibrinoid necrosis in the interlobular artery (Fig. 13), or arteriole between the afferent artery and hilar artery (Fig. 14), or venule (Fig. 15) associated with few or no immune deposits is a common feature of WG, MPA, and CSS.

Granulomatous arteritis

According to CHCC, WG manifests with granulomatous arteritis, which reveals a palisading arrangement of infiltrating macrophages (palisade cells or epithelioid cells) surrounding a necrotic lesion, including multinucleated giant macrophages (Fig. 16a, b, c). This lesion should be differentiated from the reparative or healed granulation tissue stage of necrotizing vasculitis (Fig. 17a, b) [21].

Endarteritis

Endarteritis is reflected by arterial intimal proliferation, which may follow fibrinoid necrosis in the media, thereby inducing a narrowing of the artery with subsequent organ infarct or gut perforation. This lesion consists of proliferating myointimal cells, which are presumably derived from medial smooth muscle cells and can be found in fibrinoid-necrotizing medium-sized as well as small arteritis (Fig. 18). Myointimal cells with inflammatory cell infiltration result in fibrotic scar formation in the intima, a process known as occlusive endarteritis (Fig. 19), and can be potentiated by immunosuppressant therapy. In the EU-VAS scoring system, chronic endarteritis is designated as sclerosis [7].

Arteriosclerosis (arteriolosclerosis)

Arteriosclerosis (arteriolosclerosis) is defined as a chronic lesion characterized by abnormal thickening and hardening of the walls of the arteries with a loss of elasticity. The major form of arteriosclerosis in the medium-sized or small artery in the kidney does not show atherosclerosis, in which plaques of fatty deposits can be seen, but rather a proliferation of myointimal cells and fibroelastosis in the inner walls of the arteries (Fig. 20), by which arteriosclerosis may be distinguishable from endarteritis.

Histologic grading and staging of the glomerulointerstitial lesions in rapidly progressive nephritic syndrome (Shigematsu scoring system)

In Japan, one of the groups working on "Progressive Renal Diseases from the Specially Selected Diseases of the Ministry of Health and Welfare Research Project" (1996–1998) studied rapidly progressive nephritic syndrome (WHO) in an effort to develop earlier detection methods and to produce guidelines for the effective treatment of these syndromes [15]. Based on these efforts, histologic grading (acute activity index) and staging (chronicity index) for glomerular and interstitial lesions were developed by Shigematsu et al. to help to guide treatment decisions [16]. This histologic evaluation focused on the characterization of acute and chronic lesions among intracapillary, extracapillary, and interstitial lesions, as shown in Table 1. This system precisely assesses activity such as grading and chronicity as staging for glomerular lesions and interstitial lesions using a sum score in each

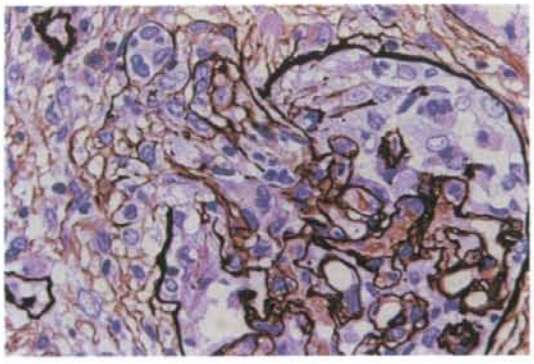


Fig. 14 Necrotizing vasculitis in an arteriole between the afferent artery and hilar artery in an MPO-ANCA-positive patient (PAM stain)

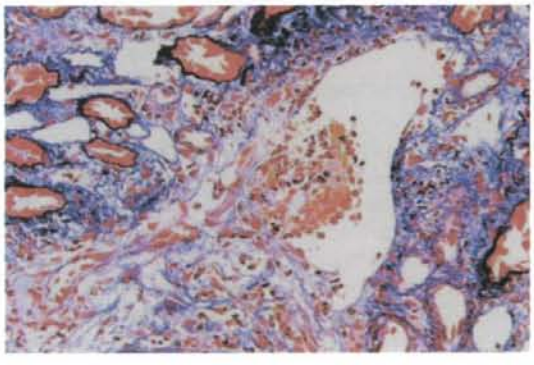


Fig. 15 Vasculitis in the venule of an MPO-ANCA-positive patient (PAM-Masson stain)

glomerular lesion, and then calculates a mean score by dividing the sum score by the total number of glomeruli [16]. However, this system is complicated and remains controversial for reproducibility, because the grades of the histological parameters are not expressed as an extent of distribution, but are expressed as the average number of grades and stages in respect to glomerular and tubulointerstitial lesions. Moreover, the vascular lesions were not considered histological parameters.

EUVAS histological classification

In the EUVAS scoring system, the severity of active as well as chronic histological parameters seen in the glomeruli are expressed as a percentage of the number of glomeruli showing a corresponding parameter to the total number of glomeruli. The histological parameter of the glomerulus includes fibrinoid tuft necrosis, extracapillary lesions (crescent), sclerosis, adhesion (synechia), and

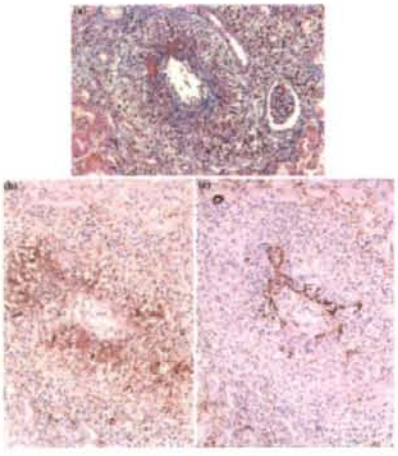


Fig. 16 Granulomatous arteritis of interlobular artery in an MPO-ANCA-positive patient. Granulomatous lesion showing palisading arrangement of the infiltrating macrophages (palisade cells), which surround a necrotic lesion, including multinucleated giant macrophages (**a**). Granulomatous lesion shows positive staining with anti-human macrophage antibody (KP1) (**b**), but negative staining for anti-smooth muscle actin, which stains only smooth muscle cells inside the artery (**c**). (**a** Masson stain, **b** immunoenzymatic method on a paraffin-embedded section using anti-human macrophage antibody (KP1), **c** immunoenzymatic method on a paraffin-embedded section using anti-smooth muscle actin)

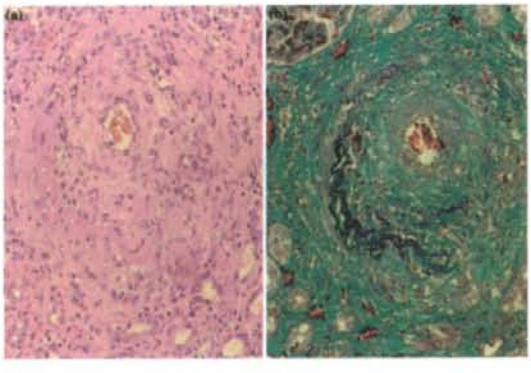


Fig. 17 Healed granulation tissue stage of necrotizing vasculitis (Arkin classification stage III) [21]. Arteritic lesion of interlobular artery in the kidney of a PN patient showing the healed granulation tissue stage in Arkin's classification (**a**) (HE stain). Elastica Masson staining shows the remaining internal elastic lamina (**b**)

others. Extracapillary lesions (crescent) are divided into circumferential (>50% of Bowman's space) and segmental (≤50% of Bowman's space), each of which is further divided into fibrous and cellular (including purely cellular and fibrocellular crescents) types. Among the number of each cellular or fibrous crescent, the numbers of crescentic glomeruli with periglomerular infiltrate and/or

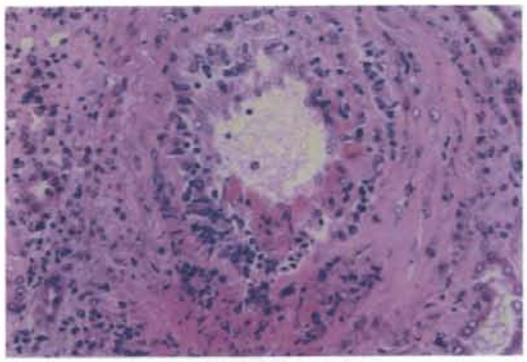


Fig. 18 Acute and active endarteritis of interlobular artery. Acute endarteritis consisting of proliferating myofibroblasts and inflammatory cells in the intima of medium-sized arteritis, which shows fibrinoid necrosis within the media (HE-stain)

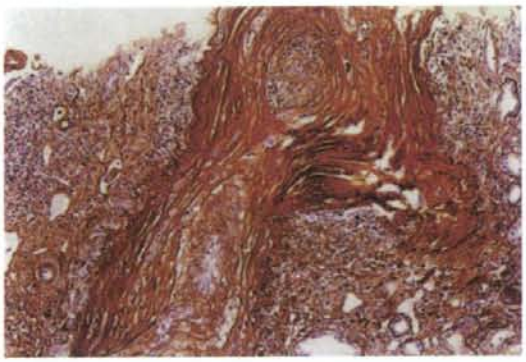


Fig. 19 Occlusive endarteritis of interlobular artery. Fibrotic scar with inflammatory cells in the intima results in arterial occlusion (PAM stain)

granulomatous reaction are calculated. Sclerosis is divided into local (small rounded area of scarring within the flocculus, <20% of the glomerulus), segmental (>20%, <80% of the glomerulus sclerosed within the flocculus), or global (>80% of the sclerosed glomerulus). Finally, among the local, segmental, and global sclerosis, the number of glomeruli with periglomerular infiltrate and granulomatous reactions is also calculated (Table 2).

Other parameters of the glomeruli are assessed dichotomously or trichotomously in the EUVAS scoring system, including mesangial proliferation [+ = more than three nuclei per peripheral mesangial area in glomeruli, which are not affected by sclerosis or extracapillary proliferation (score −/+)], mesangial matrix increase [significant increase of mesangial matrix in silver stain or PAS stain (score −/+], mononuclear/granular cell infiltration [significant: >5 cells per glomerulus in 50% of glomeruli,

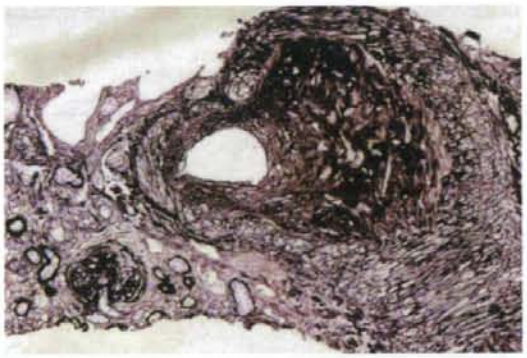


Fig. 20 Arteriosclerosis. The lesion in the medium-sized artery does not show fatty plaques, but does show proliferation of myofibroblasts and fibroelastosis in the inner walls of the arteries (PAM stain)

mononuclear cells or granulocytes in the capillary loops (including glomeruli affected by crescents or sclerosis), score + or −], and GBM thickening (thickening of the GBM, − = no thickening; + = thickening in <50% of the glomeruli; ++ = thickening in ≥50% of the glomeruli).

In evaluation of the tubulointerstitium by EUVAS, parameters including edema, focal infiltrates (− no infiltrate; + mild infiltrate; ++ dense infiltrate) or diffuse infiltrate (− no infiltrate; + mild infiltrate; ++ dense infiltrate), cell types of infiltrates (− = cell type is not present; + = cell type is present; ++ = cell type is predominantly present) for neutrophils, mononuclear cells, and eosinophils, fibrosis (− = no fibrosis; + = focal interstitial fibrosis; ++ = diffuse interstitial fibrosis), and interstitial granuloma (accumulation of epithelioid cells with or without giant cells without glomerular remnants (count the number of granuloma in the biopsy; may occur in perivascular, periglomerular and peritubular locations)).

In regard to the tubules, parameters included casts (− = no casts; + = occasional casts; ++ = numerous casts), necrosis − = absent; + = present), atrophy (− = absent, + = small foci or atrophy; ++ = extensive tubular atrophy), and intra-epithelial infiltration (infiltrate present in the tubular epithelium).

Parameters of arterial evaluation included sclerosis (intima fibrosis, splitting of elastica membrane, decrease of lumen size and/or calcification; score −/+), necrosis (presence of fibrin or fibrinoid material; score −/+), vessel wall infiltrate (score −/+), cell types of infiltrate (neutrophils, mononuclear cells, and eosinophils), vessel wall scaring, and thrombosis (score −/+/++).

In regard to the evaluation of arterioles, including afferent, efferent and medullar arterioles, parameters included hyalinosis (subendothelial deposits of PAS-positive material; score −/+), necrosis (score −/+/++), vessel wall infiltrate (score −/+), cell types of infiltrate

Table 1 Comparison of Shigematsu scoring system, EUVAS scoring system, and our proposal concerning histological parameters

Glomerulus	Shigematsu scoring	EUVAS scoring	Our proposal
Total number	○	○	○
Normal	○	○	○
Mesangial cell proliferation	×	○	○
Endocapillary hypercellularity	○	○	○
Tuft necrosis	○	○	○
Cellular/fibrocellular crescent	○	×	×
<50%	×	○	○
≥50%	×	○	○
Fibrous crescent	○	×	×
<50%	×	○	○
≥50%	×	○	○
Glomerulosclerosis			
Global	○	○	○
Segmental	○	○	○
Local	×	○	×
Collapse	○	×	○
Adhesion/synechia	○	○	○
Double contour	×	○	×
Destruction of Bowman's BM	○	×	○
Periglomerular infiltrate	×	○	×
Periglomerular granuloma	×	○	○
Fibrin thrombi	○	×	×
Mesangiolysis	○	×	×
Mesangial reticulation	○	×	×
Mesangial expansion	○	×	×
Mesangial interposition	○	×	×
Exudates into urinary space	○	×	×
Rupture of GBM	○	×	×
Extracapillary inflammatory cells	○	×	×
Parietal epithelial proliferation	○	×	×
Pseudotubularization	○	×	×
Ingrowth interstitium	○	×	×
Tubules			
Cast	×	○	×
Necrosis	×	○	○
Atrophy[a]	×	○	○
Intra-epithelial infiltrate (tubulitis)[a]	×	○	○
Destruction of tubular BM[a]	×	×	○
Interstitium			
Fibrosis	○	○	○
Infiltrate[a]			
Mononuclear cells	×	○	○
Neutrophils	×	○	○
Eosinophils	×	○	○
Granuloma	×	○	○
Edema	○	×	×
Peritubular capillaritis	○	×	○
Vascular			
Arcuate artery			
Sclerosis	×	×	○
Necrosis	×	×	○
Endarteritis	×	×	○
Cell type of infiltrate[a]			
Neutrophils	×	×	○
Mononuclear cells	×	×	○
Eosinophils	×	×	○
Thrombosis	×	○	○
Granulomatous change	×	×	○
Interlobular artery			
Sclerosis	×	○	○
Necrosis	×	○	○
Endarteritis	×	×	○
Cell type of infiltrate[a]			
Neutrophils	×	○	○
Mononuclear cells	×	○	○
Eosinophils	×	○	○
Thrombosis	×	○	○
Granulomatous change	×	×	○
Arteriole			
Hyalinosis	×	○	○
Necrosis	×	○	○
Cell type of infiltrate[a]			
Neutrophils	×	○	○
Mononuclear cells	×	○	○
Eosinophils	×	○	○
Thrombosis	×	○	○
Granulomatous change	×	×	○
Venular changes	×	×	○

[a] Evaluated by − non, + <25%; ++ 25–49%; +++ 50%≤

BM basement membrane

○ adopted

× unadopted

(neutrophils, mononuclear cells, and eosinophils), vessel wall scaring, and thrombosis (score −/+/++).

Proposal for standardization of pathological diagnosis

A score sheet for the proposed Japanese scoring system is included in Table 3. In addition to the parameters analyzed by the EUVAS systems, the present system also assesses

Table 2 EUVAS scoring system

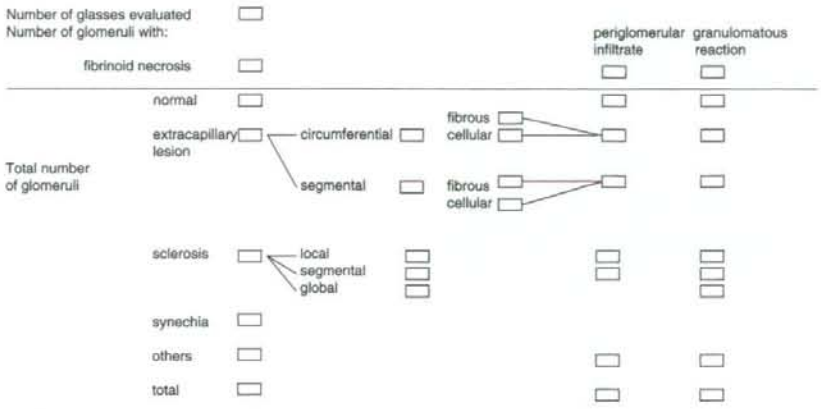
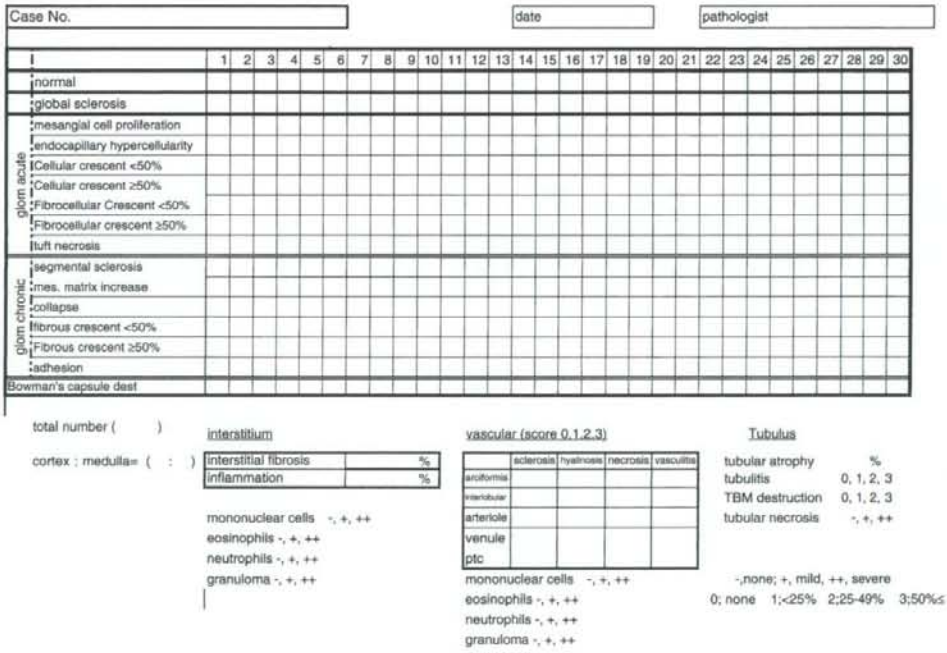


Table 3 Score sheet of our proposal



destruction of the TBM as well as the basement membrane of Bowman's capsule, the presence of granulomatous lesion in the arteries as well as the interstium, and vasculitis, including endarteritis. On the other hand, extraglomerular infiltrate, double contour of GBM and mesangial matrix increase from the EUVAS system as well as mesangiolysis, mesangial reticulation, mesangial expansion, and mesangial interposition from the Shigematsu scoring system were not adapted in order to maintain reproducibility. Extracapillary lesions, such as exudates into the urinary space, rupture of GBM, extracapillary inflammatory cells, parietal epithelial proliferation, pseudotubularization, and ingrowth interstitium from the Shigematsu scoring system, were not adopted, but were substituted by the term "tuft necrosis" or "crescent" (cellular, fibrocellular, and fibrous) in the present scoring system.

The extent of tubulointerstitial lesions, including interstitial inflammation and interstitial fibrosis with tubular atrophy, is assessed dichotomously or trichotomously in the EUVAS scoring system. The present system evaluates extended tubulointerstitial lesions more precisely. It is scored as the percentage involvement rounded to the closest 10% (i.e., <5% = 0%). Semiquantitative criteria for interstitial inflammation is evaluated according to the extent of inflammatory cells in the cortex 0 = no or trivial interstitial inflammation (<10% of unscarred parenchyma), 1 = 10–25% of parenchyma inflamed, 2 = 26–50% of parenchyma inflamed, 3 = more than 50% of parenchyma inflamed. The grade of intraepithelial infiltrate (tubulitis), destruction of TBM, and acute tubular necrosis is expressed as the extent of tubulitis (0 = <10% of unscarred parenchyma, 1 = 10–25% of parenchyma inflamed, 2 = 26–50% of parenchyma inflamed, 3 = more than 50% of parenchyma inflamed). Semiquantitative criteria for interstitial fibrosis with tubular atrophy are evaluated according to the extent of interstitial fibrosis with tubular atrophy in the cortex: 0 = no or trivial interstitial fibrosis (<5% of unscarred parenchyma), 1 = 6–25% of interstitial fibrosis, 2 = 26–50% of interstitial fibrosis, 3 = more than 50% of interstitial fibrosis. Cell types of infiltrates (− = cell type is not present; + = cell type is present; ++ = cell type is predominantly present) for neutrophils, mononuclear cells, eosinophils, and granuloma were evaluated.

Vascular lesions are evaluated on arteries and arterioles dichotomously or trichotomously in the EUVAS scoring system. The present system evaluates vascular lesions more precisely. Arterial lesions are scored based on the most severe lesions, and arcuate artery, interlobular artery, arteriole, venule and peritubular capillary are evaluated with reference to sclerosis, necrosis, vasculitis (endarteritis), and thrombosis. The grade of intimal thickening (fibrosis) is shown (−, 1 < 25%; +, 26–50%; ++, >50% thickness of intima/thickness of total vascular wall). In addition, arteriolar hyaline is also noted as present or absent. Cell types of infiltrates (− = cell type is not present; + = cell type is present; ++ = cell type is predominantly present) for neutrophils, mononuclear cells, eosinophils, and granuloma were evaluated.

Discussion

(1) Why is our proposal based on the EUVAS scoring system and how did we develop this system?

The present study outlined the histologic parameters of renal ANCA-related vasculitis in an effort to standardize the diagnosis of the disease in Japan. In order to create a new scoring system, we reviewed both Shigematsu's scoring system and the EUVAS scoring system. Shigematsu's grading and staging system consists of the average score of various glomerular and tubulointerstitial lesions and is therefore not suitable to select each glomerular and tubulointerstitial parameter for distribution as a prognostic marker. Moreover, this system does not take vascular lesions into account. The EUVAS scoring system systematically reviews the critical histological parameters. Consequently, the proposed scoring system was principally based on the EUVAS scoring system, and basic pathological parameters were selected and added to consider renal involvement in Japanese ANCA-related vasculitis (Table 1). This system uses two different types of evaluation. First, many glomerular lesions were scored quantitatively as a percentage of the total number of glomeruli. Second, other pathological parameters (e.g., some glomerular parameters as well as interstitial and vascular data) were scored dichotomously or trichotomously according to a present/absent or −, +, and ++ scale. According to an international survey study, data on inter- and intra-observer agreement gave more favorable results for the analysis of quantitative data than for dichotomous scoring systems. This result indicates that when the observers were obligated to review the biopsies more comprehensively, the inter- and intra-observer agreement was clearer than when a simple decision, such as in a dichotomous scoring system, was required [7]. Therefore, the present scoring system requires quantitative evaluation not only of glomerular lesions, but also tubulointerstitial and vascular lesions.

(2) What can the quantitative evaluation of glomerular, tubulointerstitial, and vascular lesions bring?

Semiquantitative evaluation of tubulointerstitial and vascular lesions was adopted in the present scoring system, as well as facilitated statistical evidence about the correlation between histological and clinical parameters. The EUVAS histological scoring system also showed the successful study of histopathological analysis of renal biopsies and evaluated its correlation with renal functioning. The predictive value of clinical, serological, and histological parameters for the renal outcome were analyzed by multivariate analysis, resulting in an index that is valid for clinical use. Specifically, the formula for the estimation of renal function at 18 months is as follows: GFR (glomerular filtration rate) 18 (ml/min) = 17 + 0.71 × GFR0 (ml/min) + 0.34 × fibrinoid necrosis (%) + 0.33 × segmental crescents (%) ($r^2 = 0.60$; standard deviation = 19 ml/min) [12].

(3) Why should the vascular lesion be evaluated respecting the level of artery?

Vascular lesions in each arcuate artery, interlobular artery, and arteriole need to be evaluated in the present scoring system, because a differently affected level of renal

vasculature in ANCA-related vasculitis between Europe and Japan has been noticed. Histological evidence of small-vessel arteritis in ANCA-related vasculitis is rare (about 15% of cases) even with a lower prevalence of medium-vessel arteritis in Europe. In the recent EUVAS MEPEX (randomized trial of adjunctive therapy for severe glomerulonephritis in ANCA-related systemic vasculitis-intravenous administration of methylprednisolone versus plasma exchange) study of 100 renal biopsies, the frequency of small-vessel arteritis was 11%, and the frequency of medium-sized arteritis was 4% [13]. Preliminary data from 72 cases of MPO-ANCA-related vasculitis from a Japanese study group detected 21 out of 72 cases (29.1%), including arteriolar vasculitis (13 out of 72 cases, 18.1%), interlobular arteritis (8 out of 72 cases, 11.1%), and arcuate arteritis in 1 case. Although the definition of the term "medium-sized artery" in the kidney is still controversial, it suggests possible immunological and morphological differences between Japanese and European populations as well as potential differences in genetic and environmental factors and/or pathogenetic morphogenetic mechanisms. PN mainly affects medium-sized vessels and can be differentiated from WG, MPA, and CSS by the absence of glomerular lesions according to CHCC definitions [2]. However, there have been a few reports of large vessel involvement in ANCA-related vasculitides in Japan, as shown in Fig. 12, and in North America and Europe [22].

(4) Why should the presence of granulomatous lesion in the artery and in the interstitium be evaluated?

The presence of granulomatous lesions in the arteries as well as in the interstium was also evaluated in the present system. The extent of destruction of the TBM as well as of the basement membrane of Bowman's capsule is also assessed, because this destruction induces a granulomatous lesion, and the grade of tubulitis and TBM destruction was correlated with the titer of C-reactive protein (CRP) (our preliminary data; abstract in the International Symposium of Vasculitides, September 29, 2007, Tokyo). According to CHCC definitions, granulomatous inflammation of an artery or perivascular interstitial area is found in WG, whereas pauci-immune necrotizing glomerulonephritis is common to both MPA and WG [2]. Therefore, the principal difference between these two entities may be the presence of granulomatous inflammation in the latter disease; however, according to our experience in Japan, this histological criterion does not help to discriminate WG from MPA. Indeed, in almost all cases, patients with positive MPO-ANCA showed a renal lesion, which is essentially indistinguishable from patients with classical WG showing an extrarenal granulomatous lesion in the upper respiratory tract or in the lung. In terms of the differential diagnosis of WG versus MPA, a consensus stepwise algorithm has been developed using criteria from the American College of Rheumatology (ACR) and CHCC. It can successfully categorize ANCA-positive patients into a single classification [23]. Whether the presence of a granulomatous lesion is a hallmark of WG remains to be solved in the future. CSS, allergic granulomatosis and angiitis, is often found in the context of vascular and extravascular granulomatosis containing a large number of eosinophils. Clinically, bronchial asthma and eosinophilia are found. Renal involvement is present in 25% of all cases, reflecting the relatively benign course when compared with MPA [24]. The presence of these criteria, including eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing and granulomatous arteritis affecting small to medium-sized vessels, asthma, and eosinophilia, yields a sensitivity of 85% and a specificity of 99.7% for the diagnosis of Churg-Strauss arteritis [25]. This is also a reason to evaluate the presence of granulomatous lesion in the arteries as well as in the interstium.

(5) Is there any difference between MPO-ANCA- and PR3-ANCA (ANCA directed against pronase 3 as determined by ELISA)-related vasculitis concerning the histology and the prevalence in Asia and Europe?

Knowledge of the differences in renal histopathology between MPO-ANCA- and PR3-ANCA-related vasculitis or MPA and WG is relatively limited, although distinct histologic differences may help to establish a more definite diagnosis and may give insights into the pathogenesis of ANCA-related vasculitis. One study of 173 renal biopsies reported that the characteristics of chronic injury were more prevalent in biopsies from patients with MPA than with WG, which suggests that the pathogenesis and/or course of these diseases may be distinct [11]. Franssen et al. reported that patients with PR3-ANCA positivity had more fibrinoid necrosis and a higher activity index than those with MPO-ANCA positivity and that patients with MPO-ANCA had more glomerulosclerosis and a higher chronicity index [26]. By contrast, other studies have reported contradictory results or no differences between these groups [27, 28]. MPO-ANCA-related vasculitis is prominent in Japan and China, whereas PR3-ANCA is common in Europe. Patients with MPO-ANCA-positive WG are often found in the Chinese population and have been analyzed with regard to the histological differences between MPO- and PR3 ANCA-positive WG [29]. Two nationwide Japanese surveys demonstrated that the prevalence of patients with WG is very low compared with that of patients with microscopic polyangiitis (MPA) [30] and/or renal limited vasculitis (RLV) [31]. In Japan, the annual prevalence (i.e., the estimated number of patients treated in 1997) of WG is only 2.3 per million, whereas that of MPA and/or RLV is approximately 13.8 per million [30, 31].

Furthermore, MPO-ANCA was identified in 79–93% of patients with MPA and/or RLV in Japan, whereas reports from Europe described a percentage of 44–69% [11, 32–35]. Fujimoto et al. [36] reported that the estimated annual incidence of primary renal vasculitis in Miyazaki Prefecture was 14.8 (95% CI 10.8–18.9) and 44.8 (95% CI 33.2–56.3) per million adults (>15 year old) and seniors (>65 year old), respectively. Another study of rapidly progressive glomerulonephritis in Japan characterized subtypes as p-ANCA-related glomerulonephritis (67.3%), c-ANCA-related glomerulonephritis (4.7%), ANCA-negative pauci-immune type glomerulonephritis (6.4%), anti-GBM glomerulonephritis (8.8%), and lupus nephritis (8.2%) [15].

(6) Problems remain to be solved in the future

A disease condition presenting with only pauci-immune focal necrotizing glomerulonephritis, crescentic glomerulonephritis, or arteritis in the absence of other organ system involvement is generally classified as "renal-limited" vasculitis (RLV). In Japan, laboratory testing for ANCA is supported financially by national insurance. Thus, many more patients are being diagnosed and treated in an early stage of disease, resulting in higher rates of remission before the full clinical course becomes apparent. Later clinical manifestations may follow, suggesting the onset of vasculitis in other systemic organs. It has not yet been determined whether combined systemic vasculitis or late onset of systemic vasculitis occurs more frequently when RLV patients show not only necrotizing glomerulonephritis, but also medium-sized or small arteritis. These problems remain to be solved in the future.

In Japan, the histology-based therapeutic choice for ANCA-related glomerulonephritis is still uncertain. Sakai et al. reported the impact of a histologic scoring system, including the distribution and stage of crescents, and grade of tubulointerstitial lesions for an outcome prediction, but it is insufficient to guide the choice of therapy [15]. Thus, a future study to characterize optimal treatment regimens based on histological distinctions of ANCA-related vasculitis would be of benefit. This classification will also be applied for anti-GBM nephritis (nephritis in Goodpasture syndrome) and idiopathic crescentic glomerulonephritis.

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特集：IgA 腎症の基礎と臨床

IgA 腎症の病理学的分類(国際分類の基本的考え方も含めて)

城　謙輔

はじめに

IgA 腎症は，病理形態学的に糸球体メサンギウム基質の拡大，ときに半球状沈着物が観察され，種々の程度のメサンギウム細胞増殖を伴い，蛍光抗体法でメサンギウム領域に IgA 優勢の沈着を認める疾患をいう。IgA 腎症は腎生検によって初めて診断される疾患で，そのため腎生検の組織所見が IgA 腎症の治療の出発点となる[1]。

IgA 腎症の組織学的分類は，わが国では厚生労働省・日本腎臓学会合同による組織学的予後分類(2002 年)を基準としてきた[2,3]。この組織学的予後判定基準は，病変の多彩な IgA 腎症を組織学的に分類し，それを臨床予後と関連づけ，治療の選択の参考にする観点からこれまでに重要な役割を果たしてきた。しかし，この分類は，あくまで臨床予後を予測するための組織分類であり，治療方針を立てるための組織分類でなかったと言える。その理由は，治療により改善が見込まれる活動性病変と，主に病期を決定する慢性病変とが分けられておらず，したがって，この分類において予後不良を予測する組織学的分類群に対して強力な治療を推奨することには結びつかないからである。治療方針を立てるにあたり，IgA 腎症の活動性病変と慢性病変に関する定量的把握が必要であり，それを考慮した新しい組織分類が望まれてきた。

2005～2007 年厚生労働省難治性疾患克服対策研究事業進行性腎障害に関する調査研究班(主任研究者　富野康日己)の IgA 腎症分科会(分担研究者　川村哲也)において，IgA 腎症の腎病理所見と予後の関連に関する後ろ向き・前向き多施設共同研究が始まり，組織病変と臨床予後との関連を再検証し，科学的根拠に基づいた組織分類を作成するプロジェクトが組まれた。時を同じくして，国際 IgA 腎症ネットワーク(International IgA Nephropathy Network)と世界腎病理協会(Renal Pathology Society)の共同により，IgA 腎症の国際臨床病理分類に関する研究プロジェクトが組まれ，2005 年 9 月にオックスフォード・Magdalen カレッジにて第 1 回合同会議が持たれた。

本稿では，わが国において旧分類から新分類(案)に至ったこれまでの経緯ならびに国際 IgA 腎症臨床病理組織分類委員会の経過を報告し，IgA 腎症の病理組織分類に関する問題点と今後の見通しを解説する。

IgA 腎症診療指針「第 2 版」(旧分類)における予後判定基準

IgA 腎症の組織学的予後分類については，これまでに幾多の提案がなされている[4~9]。大まかに lumped(塊状)system と split(分割)system に大別できる。前者の例として，Haas 分類[4]，Lee 分類[5]，片渕分類[6]があげられ，それらは臨床予後を予測するためには再現性のある分類法であるが，個々の症例での特徴が出にくく，治療指針の判断につながりにくい[7]。一方，後者の例として，重松分類[8]，国立病院機構腎ネットワーク分類[9]にみられるように，急性活動性病変と慢性病変，そして，糸球体病変と間質病変が個別に扱われ，それぞれの病変の程度がスコア化されている。しかし，この分類法は操作が煩雑であり診断者間での再現性の検証が必要となる。

わが国では，厚生労働省特定疾患・進行性腎障害研究班 IgA 腎症分科会において，IgA 腎症患者の腎生検施行の時点での組織学的予後判定基準が設定され，以下のごとく定義されている[2,3]。

まず，臨床的予後を以下の 4 群に分けた。

①予後良好群：透析療法に至る可能性がほとんどないもの

Proposal for a new histological classification of IgA nephropathy in Japan and a preliminary report of the international clinico-pathological classification of IgA nephropathy

国立病院機構千葉東病院臨床研究センター腎病理研究部

②予後比較的良好群：透析療法に至る可能性が低いもの
③予後比較的不良群：5 年以上・20 年以内に透析療法に移行する可能性があるもの
④予後不良群：5 年以内に透析療法に移行する可能性があるもの

そして，上記の臨床的予後が以下の腎生検光顕標本による組織学的予後判定基準に基づいて分類されている。

①予後良好群：軽度のメサンギウム細胞増殖と基質増加のみ。糸球体硬化，半月体の形成，ボウマン嚢との癒着は認めない。尿細管，間質，血管に著変を認めない。

②予後比較的良好群：軽度のメサンギウム細胞増殖と基質増加を認める。糸球体の硬化，半月体の形成，ボウマン嚢との癒着を認める糸球体が全生検糸球体の 10 %未満である。尿細管，間質，血管に著変を認めない。

③予後比較的不良群：中等度のびまん性メサンギウム細胞増殖と基質増加を認める。糸球体の硬化，半月体の形成，ボウマン嚢との癒着を認める糸球体は全生検糸球体の 10 %以上 30 %未満である。尿細管の萎縮は軽度で，間質では一部の硬化糸球体周囲以外には炎症細胞浸潤は軽度である。血管には軽度の硬化性変化を認める。

④予後不良群：高度のびまん性メサンギウム細胞増殖と基質増加を認める。糸球体の硬化，半月体の形成，ボウマン嚢との癒着を認める糸球体は全生検糸球体の 30 %以上である。さらに硬化部位を加算し全節性硬化に換算すると，その硬化率は全糸球体の 50 %以上である。また，代償性肥大を示す糸球体をみることがある。尿細管萎縮および間質細胞浸潤は高度で，線維化も高度である。一部の腎内小動脈壁に肥厚あるいは変性を認めることがある。

なお，腎生検の組織所見に加えて，血圧，血清クレアチニン，クレアチニンクリアランス，尿蛋白量などの値に悪化傾向が認められた場合は，予後判定の重要な補助手段になる。また，経過中に他の群に移行することがあることを付記している。

上記の記述からわかることは，第一に，臨床予後が透析導入で判断されているが，この組織学的予後分類の臨床予後が実証されているわけではない。第二に，組織の病変パラメータでは，糸球体硬化，半月体形成，ボウマン嚢との癒着の 3 つの病変パラメータだけが，10 %と 30 %を区切りに定量的な評価を受けているが，メサンギウム細胞増殖，尿細管・間質障害の程度と血管硬化の程度に関しては定量的評価を受けていない。また，半月体病変が急性活動性半月体(細胞性＋線維細胞性)と慢性半月体(線維性半月体)が区別されていないこと，ときに蛋白尿の増加の裏付けとなる糸球体毛細血管係蹄の管内活動性病変が評価されていないこと，そして，ボウマン嚢との癒着が狭義の癒着病変なのか線維性小半月体を含む癒着なのかが明らかにされていないことなどである。このように，治療により病変の改善が望まれる急性活動性病変と治療による介入が望まれない慢性病変とに区別されていないため，治療選択の指針としてはこの予後分類が不十分であることがわかる。また，メサンギウム細胞増殖，糸球体硬化率，半月体形成率，間質・血管病変が並列的に扱われているが，必ずしもこれらの病変が並行して進展していくとは限らず，その際，何を判定基準に定量的分類をしてよいのかが明確ではない。そのため，この判定基準の解釈には各施設や個人の間で相違があり，「糸球体硬化」「半月体形成」「ボウマン嚢との癒着」のうち，最も出現頻度の高い病変の総糸球体数に対する割合(%)を判定基準として採用するという考え方(以下，OR 分類，split system)と，3 つの病変のいずれかを呈する糸球体を加算し，総糸球体数に対する割合(%)を判定基準として採用するという考え方(以下，AND 分類，lumped system)の 2 つの異なる解釈が可能であり，それによる病変の定量的診断の手法が統一されていなかった。

国際的基準に沿った IgA 腎症の病変パラメータの選択

時を同じくして，国際 IgA 腎症ネットワーク(International IgA Nephropathy Network)と世界腎病理協会(Renal Pathology Society)の共同により，IgA 腎症の臨床病理分類に関する研究プロジェクトが計画され，2005 年 9 月にオックスフォード・Magdalen カレッジにて第 1 回合同会議が持たれた。その会議では，IgA 腎症の病理組織評価に必要な病変パラメータを選択し，その病変の定義，さらにスコア・シートの作成により定量的評価法が決められた(**表 1**)[10,11]。これまでに，世界から収集された 300 症例あまりの IgA 腎症症例がこの共通の評価基準に従って診断され，収集された臨床病理データにより，2008 年 4 月の第 2 回合同会議にて組織学的分類の原案が作成される予定である。わが国の IgA 腎症の組織学的評価も，この基準から逸脱しないように，以下の病変パラメータを選択して，後ろ向き多施設共同研究による組織学的評価にあたった。その病変パラメータとして，球状硬化，半月体(細胞性，線維細胞性，線維性)，癒着，虚脱，分節状硬化・硝子化，メサンギウム細胞増殖，管内性炎症細胞浸潤，糸球体毛細管係蹄壊死を選択し，その病変を認める糸球体の数を算出し全糸球

表 1 IgA 腎症の臨床病理分類に関する第 1 回オックスフォード会議により定められた定量的組織評価基準(スコア・シート)

	Column A			IgA nephropathy Working Group score sheet		
Mesangial cell hypercellularity		Total	Mesangial score			
no hypercellularity(0)				Case Number		
mild(1)(4～5 cells)				Scorer		
moderate(2)(6～7 cells)				Date		
severe(3)(≧8 cells)						
Total number of scorable glomeruli		A	B >>	Mean mesangial score(B divided by A)		
Indeterminate			>>>>>>>>>>	Indeterminate mesangial cellularity due to :	Total	
Total number of glomeruli				Global sclerosis		
	Column B			Advanced segmental sclerosis		
Normal glomerulus				Ischemic/collapsed		
Segmental sclerosis				Incomplete mesangial area		
Adhesion				Crescent only(type in col. B)		
Ischaemia/collapse						Column C
Endocapillary hypercellularity				Tubular atrophy(%)(score to nearest 10 %)		
Segmental				Interstitial fibrosis(%)(score to nearest 10 %)		
Global				Interstitial inflammation(%)(score to nearest 10 %)		
GBM duplication				check in scarred areas only		
Necrosis				in scarred and non-scarred		
Extracapillary lesions-cellular				Arteriosclerosis interlobular arteries None present		
Tiny focus(<10 %)				No intimal thickening		
Small focus(10～25 %)				intimal thickened and<25 % media		
Crescent(26～50 %)				intimal thickened and 25～50 % media		
Crescent(>50 %)				intimal thickened and>50 % media		
Extracapillary lesions-fibrocellular				arcuatel arteries & larger None present		
Tiny focus(<10 %)				No intimal thickening		
Small focus(10～25 %)				intimal thickened and<25 % media		
Crescent(26～50 %)				intimal thickened and 25～50 % media		
Crescent(>50 %)				intimal thickened and>50 % media		
Extracapillary lesions-fibrous				Arteriolar hyalinosis present		
Small focus(10～25 %)				absent		
Crescent(26～50 %)				Other		
Crescent(>50 %)						

体数に対する割合を %で記載した。また，間質病変は，腎皮質における炎症細胞浸潤の拡がりと間質幅(間質領域/糸球体と大血管を除く腎皮質面積)を 10 %ごとの %で記載し，血管病変では，小動脈(多くは小葉間動脈)内膜の線維性肥厚の程度(内膜の厚さ/全層の厚さ×100：<25 %，25～50 %，50 %<)と細動脈内膜の硝子化の有無を記載した。

IgA 腎症の腎病理所見と臨床予後との関連に関する後ろ向き多施設共同研究の成果

全国 16 の腎専門施設から 287 症例の臨床データと腎生検標本が収集された(謝辞に参加施設を掲載)。症例登録基準は，腎生検にて IgA 腎症と診断された症例，本研究への登録に文書による同意が得られた症例，透析導入例あるいは腎生検後 5 年以上経過を観察し得た症例，そして，腎生検以後の治療内容(ステロイド薬，レニン・アンジオテンシン系阻害薬の使用など)が明らかな症例のうち，腎生検にて総糸球体数が 10 個以上の症例であった。

上述の病変パラメータを定量的に評価し，臨床予後として透析導入率への影響をロジステイック解析で行ったところ，5 年以内の透析導入率と 5 年から 10 年以内でのどちらの透析導入率に対しても，メサンギウム細胞増殖の程度と癒着は有意な影響をもたず，全半月体形成率と球状硬化率において有意な影響を認めた[12]。さらに，糸球体硬化を全節性(球状)硬化と分節性硬化に分け，全半月体を活動性半月体(細胞性＋線維細胞性)と慢性(線維性)半月体に分け，ロジステイック解析を行ったところ，生検後 5 年以内の透析導入率では，活動性半月体に有意な影響力はなく，分節性硬化率ならびに線維性半月体形成率と球状糸球体硬化率に有意な影響を認めた。一方，5 年から 10 年以内での透析導入率では，球状糸球体硬化率とともに活動性半月体形成

率による影響を認めたが，分節性硬化率ならびに線維性半月体形成率には影響を受けなかった[12]。このように，5年以内の透析導入率には，全節性硬化，分節性硬化，線維性半月体などの慢性病変の評価が主体であるが，5年以後の透析導入率を考慮すると，急性活動性半月体形成の評価が必要であることがわかった。

以上のことから，活動性糸球体病変として，細胞性半月体，線維細胞性半月体，毛細血管係蹄壊死(**図 1**a, b)が，慢性糸球体病変として，全節性(球状)糸球体硬化，分節性糸球体硬化，線維性半月体(**図 2**a, b)が，評価の対象となる病変パラメータとして選ばれた。上記の国際会議で決められた定義を抜粋して掲載する(**表 2**)。一方，国際分類に従った狭義の癒着病変は予後に有意な影響力を持たないという理由で除外された(**図 3**a)。しかし，癒着病変はボウマン嚢円周の1/4以下の局所で，慢性管外性病変である線維性小半月体との鑑別が困難な場合があり(図 3b)，慢性病変にカウントされるか否かについて現在検討中である。

a|b

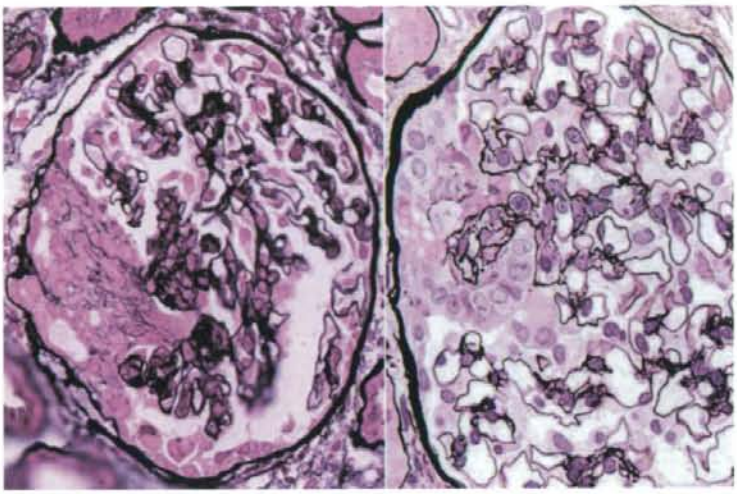


図 1　IgA 腎症の活動性病変としての細胞性半月体(a)と糸球体毛細血管係蹄壊死(b)(PAM 染色)

a|b

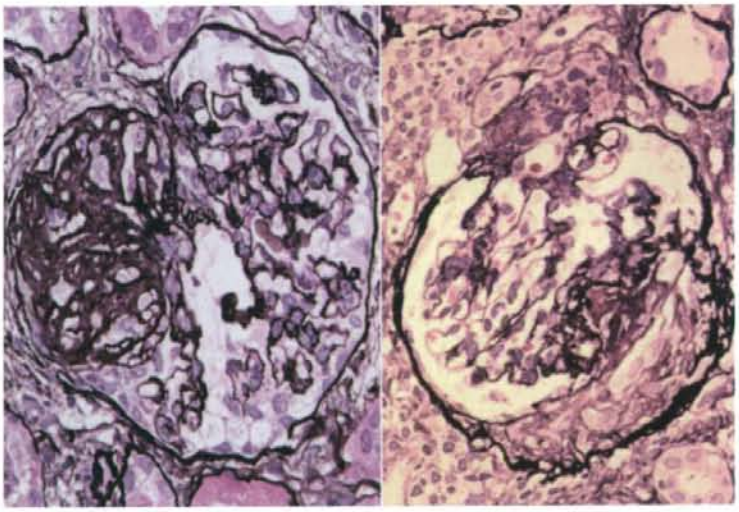


図 2　IgA 腎症の慢性病変としての分節性硬化糸球体(a)と線維性半月体(b)(PAM 染色)

新分類への提案

後ろ向き研究に用いた287例において，「糸球体硬化」「半月体形成」「ボウマン嚢との癒着」の3つの病変パラメータを用いて，10％と30％を区切りとした旧分類でのOR分類(split system)をすると，1/Crの経年的変化率において，Ⅰ群(予後良好群)，Ⅱ群(予後比較的良好群)，Ⅲ群(予後比較的不良群)の区別がつかないことが判明した[12]。さらに，病変パラメータを定量的に診断するという実践的現場においては，それぞれの病変パラメータをもつ糸球体数の全糸球体数に対する割合をいちいち計算するという作業は一般に受け入れられにくい。このような理由から，新分類においては，活動性糸球体病変として細胞性半月体，線維細胞性半月体，毛細血管係蹄壊死が，そして慢性糸球

表 2 組織学的重症度分類(案)に用いられた活動性，慢性病変の定義

A．糸球体における病変の定義
びまん性(diffuse)：50 %以上の糸球体に病変の分布を示す。
巣状(focal)：50 %未満の糸球体に病変の分布を示す。
球状(global)：糸球体毛細血管係蹄の 50 %以上を巻き込む病変(分節状と球状硬化の定義に対して下記参照)
分節状(segmental)：糸球体毛細血管係蹄の 50 %未満を巻き込む病変(少なくとも糸球体毛細血管係蹄の半分が保存されている。)(分節状と球状硬化の定義に対して下記参照)
管内性細胞増殖(endocapillary hypercellularity)：糸球体毛細血管係蹄の管腔内の細胞数が増加し，管腔の狭小化を引き起こしている細胞増殖
核破砕(karyorrhexis)：アポトーシスや濃縮/断片化した核の存在
壊死(necrosis)：フィブリンの滲出や核破砕を伴って糸球体基底膜が崩壊すること
糸球体基底膜 2 重化(GBM duplication)：糸球体基底膜が 2 重の輪郭を示し，管内性増殖を伴っていてもいなくてもよい。
メサンギウム基質増生(increased mesangial matrix)：メサンギウムの細胞外基質の増加で，その毛細血管管腔間の幅が少なくも 2 つの分節においてメサンギウム細胞核 2 個以上を超える。
硬化(sclerosis)：細胞外基質の増加により毛細血管腔が閉塞した病変を指し，硝子化を伴っていてもいなくてもよい。また，泡沫細胞があってもよい。
癒着(adhesion)：糸球体毛細血管係蹄とボウマン嚢の間の連続した領域を指し，管外性病変や分節状硬化病変の領域から隔離している(原文)。その後，以下の定義に変化しているが最終案には至っていない。"ボウマン嚢円周の 20 %以下で，糸球体毛細血管係蹄とボウマン嚢間の連続した細胞外基質の領域を指す。"
管外病変(extracapillary lesions)は以下の亜型に分かれる。
　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があり，その成分として細胞が 50 %以上ある病巣をいう。さらに，この病巣による糸球体円周の%により分類される(<10 %，10～25 %，26～50 %，>50 %)
　管外性線維細胞増殖または線維細胞性半月体(Extracapillary fibrocellular proliferation or fibrocellular crescent)：細胞と細胞外基質の組み合わせ(細胞が 50 %以下で基質が 90 %以下)により覆われたボウマン嚢円周の 25 %より大きい病巣をさす。この病巣はしばしばボウマン嚢の破壊を伴う。虚血性廃退性糸球体は除く。
　管外性線維増殖または線維性半月体(Extracapillary fibrous proliferation or fibrous crescent)：ボウマン嚢円周の 10 %以上が 90 %以上の細胞外基質の成分によって覆われている病巣。さらに，この病巣による糸球体円周の%により分類される(<10 %，10～25 %，26～50 %，>50 %)(原文)。
小半月体(small crescent)：糸球体円周の 25 %以下を巻き込む管外性病巣 1 つをさす(原文)。
メサンギウム細胞増殖は以下の亜型に分類される。
　正常(normal)：メサンギウム基質に 3 個以下のメサンギウム細胞が見られる。
　軽度(mild)：メサンギウム基質に 4～5 個のメサンギウム細胞が見られる。
　中等度(moderate)：メサンギウム基質に 6～7 個のメサンギウム細胞が見られる。
　高度(severe)：メサンギウム基質に 8 個以上のメサンギウム細胞が見られる。
　注意：最も細胞に富む分節を評価することにより個々の糸球体が評価される。
分節状硬化(segmental sclerosis)：糸球体毛細血管係蹄の一部(すべての係蹄を侵さない)に硬化が認められる。
球状硬化(global sclerosis)：糸球体毛細血管係蹄の全体が硬化した病巣
虚脱/虚血糸球体(collapsed/ischemic glomerulus)：糸球体毛細血管は虚脱し，ボウマン嚢の肥厚やボウマン腔の線維化を伴う場合がある。

B．尿細管間質病変の定義
尿細管萎縮(tubular atrophy)：尿細管基底膜が不規則に肥厚し，尿細管周径が減少する病巣。腎皮質において，被膜下の領域を除いた尿細管領域の%でスコア化される。スコア化においては 10 %単位で四捨 5 入して評価される(例えば<5 %＝0 %)。
間質線維化(interstitial fibrosis)：被膜下領域を除く腎皮質の領域で，尿細管領域を除いた細胞外基質の増加病変を指す。スコア化においては 10 %単位で四捨五入して評価される(例えば<5 %＝0 %)。
間質の炎症(interstitial inflammation)：腎皮質の間質領域の炎症細胞浸潤を指す。スコア化においては 10 %単位で四捨五入して評価される(例えば<5 %＝0 %)。炎症が萎縮尿細管に限局しているかどうかを付記する。
その他の尿細管病変(additional tubular lesions)：以下の病変があれば付記する。20 %以上の尿細管において尿細管管腔が完全に赤血球によって充満することによる多量の赤血球の存在があれば付記する。その際，円柱を伴う場合がある。
急性尿細管傷害(acute tubular injury)：尿細管基底膜の肥厚を伴うことなしに尿細管上皮が単純化することによって定義される近位尿細管上皮の病変を指す。

C．血管病変の定義
動脈病変(arterial lesions)：最も顕著な病変によってスコア化される。小葉間動脈かそれより大きな動脈は別個にスコア化される。内膜肥厚は中膜の肥厚と比較することにより以下に段階的に分類される(<25 %，25～50 %，>50 %)。
細動脈病変(arteriolar lesions)：硝子化病変以外の細動脈硬化があれば付記する。
細動脈硝子化(arteriolar hyaline)：有るか無しかを記載する。
注意書き：他の血管病変があればその他の枠に記載する。

a | b

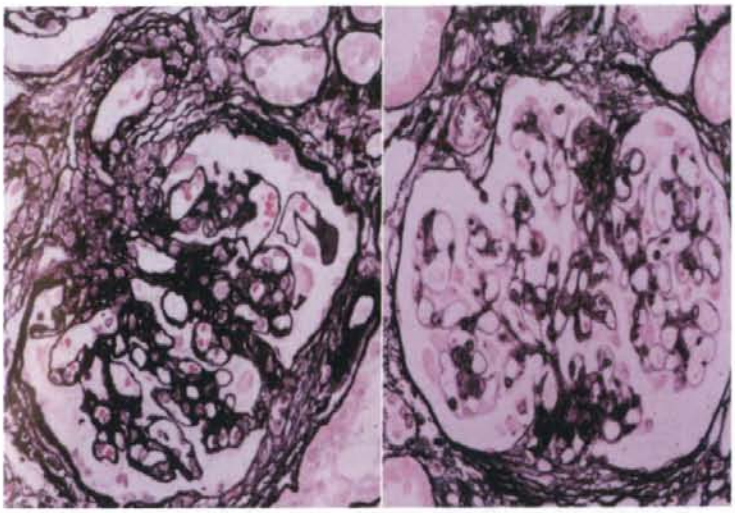


図 3　狭義の意味での癒着病変で，慢性管外性病変を伴っていない(a)。線維性半月体で慢性管外性病変を伴っているが，ボウマン嚢周囲 1/4 以下であるため，国際基準では小半月体として定義される(b)。

表 3　組織学的重症度分類(案)

組織学的重症度	球状硬化＋分節性病変*を有する糸球体/総糸球体数	急性病変のみ	急性病変＋慢性病変	慢性病変のみ
Grade I	0＜＜25 %	A	A/C	C
Grade II	25 %≦＜50 %	A	A/C	C
Grade III	50 %≦＜75 %	A	A/C	C
GradeIV	75 %≦	A	A/C	C

*急性病変(A)：細胞性半月体，線維細胞性半月体，係蹄壊死
慢性病変(C)：全節性糸球体硬化，分節性糸球体硬化，線維性半月体

表 4　組織学的重症度(grade Ⅰ～Ⅳ)からみた症例数の度数分布と臨床予後

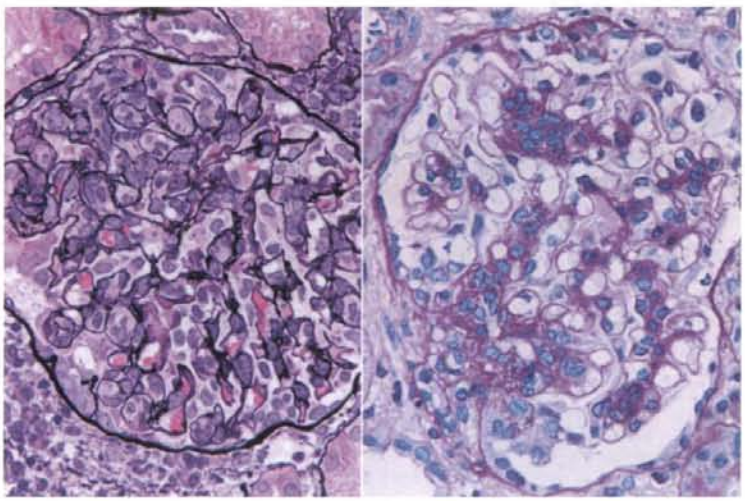
組織学的重症度	球状硬化と分節性病変*を有する糸球体/総糸球体数	なし(%)	急性病変のみ(%)	急性病変＋慢性病変(%)	慢性病変のみ(%)	合計	透析導入(%)
I	0 %	33	—	—	—	33	1(3)
	0 %＜＜25 %	—	4	33	81	118	10(8)
II	25 %≦＜50 %	—	0	30	45	75	12(16)
III	50 %≦＜75 %	—	0	21	21	42	13(31)
IV	75 %≦	—	0	10	9	19	13(68)
	合計	33(11)	4(1)	94(33)	156(54)	287	49(17)

*分節性病変：細胞性半月体，線維細胞性半月体，係蹄壊死，線維性半月体，分節性硬化

体病変として，全節性糸球体硬化，分節性糸球体硬化，線維性半月体のいずれかの病変がある糸球体が，全糸球体数の何％あるかを基準として評価する方法をとった。それは，最近の Lee の分類法にも類似している[13]。評価の対象となる上記の病変をもつ糸球体の全糸球体に対する割合を 25 %，50 %，75 %で区切り，組織学的重症度 grade I，II，III，IV(新分類案)とした(**表 3**)。メサンギウム細胞増殖の程度は，前述の後ろ向き研究において透析導入率に影響しないという理由から grade 分類には考慮されていない。一方，上記の急性(活動性)病変と慢性病変の区別は新分類に盛り込まれている。287 症例中，それぞれの頻度分布をみると，grade I から grade IV を通じて，病変なし，急性病変のみ，急性病変と慢性病変，慢性病変のみが，それぞれ，11 %，1 %，33 %，54 %となり，急性病変，急性病変と慢性病変，そして，慢性病変に区別して分類する根拠を示している。そのなかで grade I が 287 症例中の 151 例(53 %)を占め，早期の適正治療の重要性を示唆している(**表 4**)[12]。また，grade I，II，III，IV のそれぞれにおける透析導入率は 7 %，16 %，31 %，68 %で，grade I に対する grade II，III，IV の odds 比は，2.4，5.7，27.0 で有意性をもって上昇している(**表 5**)[12]。

表 5 組織学的重症度(grade Ⅰ～Ⅳ)からみた透析導入の予測度(オッズ比で評価)

重症度(Grade)	症例数	透析導入例(%)	Odds ratio(OR) vs. Grade Ⅰ	p-value
Ⅰ	151	11(7)	1	
Ⅱ	75	12(16)	2.4	<0.05
Ⅲ	42	13(31)	5.7	<0.05
Ⅳ	19	13(68)	27.0	<0.001



a|b

図 4 IgA 腎症の管内活動性病変(a)とメサンギウム細胞増殖(b)
両病変とも新分類を決定する病変には選択されていない。

今後の課題

間質病変と血管病変への評価が置き去りにされているが，再現性のある定量的評価法が定まらない現時点では，新分類の病変パラメータから除外されている。今後の検討課題であるが，糸球体の慢性病変の形成率に比較してアンバラスに間質病変あるいは血管病変が目立つ場合は備考に付記することにした。この新分類(案)が，小児の IgA 腎症に適応されるかどうかも問題となる。小児においては，管内活動性病変(**図 4**a)やメサンギウム細胞増殖(図 4b)がそれぞれ前景となって臨床症状に影響し，それに応じた治療が選択される。しかし，新分類においては上記の 2 つの病変は，臨床予後(透析導入率)に影響しないという理由で分類を決定する病変パラメータには入れられていない。その点，オックスフォード会議で採用された IgA 腎症の病変パラメータそれぞれについて定量的評価をする分類(OR 分類あるいは split system)が，小児，成人を問わず治療方針の決定にはより詳細な情報を与えてくれる[10,11]。一方，新分類のように病変を合わせて評価する分類法(AND 分類あるいは lumped system)は，再現性があり臨床予後(透析導入)を予測できる観点から今回採用されたが，上述のように個々の症例での特徴が出にくく，治療方針に寄与する観点からは問題が残る。予後予測と治療指針の 2 つの目的を満足する組織学的分類の難しさを痛感する。

組織学的評価は，あくまで組織学的重症度分類(grade Ⅰ～Ⅳ)として提示し，旧分類のように組織学的予後判定基準とはしていない。その理由の一つとして，両側の腎臓で糸球体数が約 200 万個あるなかから腎生検での糸球体数 10～20 個で個体全体の臨床データ(蛋白尿，腎機能)を推し量るには限界があることがあげられる。また，生検時の蛋白尿，腎機能，血圧の程度やそれらの持続期間，そして，治療による臨床データの改善の有無など，病理所見のほかに臨床

情報を加えた総合的評価が最終的に臨床予後に影響することは疑いもない。治療の選択は，病理所見だけにとどまらず，臨床データを含めた総合的な臨床予後リスクの層別化を実現することで決定されるべきであり，その最終案を現在検討中である。

おわりに

IgA 腎症の診療において，腎生検は IgA 腎症を診断するのみならず，治療方針の決定，予後の予測，そして，治療反応性の検証に重要な情報をもたらす検査法である。IgA 腎症の適正な治療法に対して科学的根拠を持つ証拠を得るために，国際的な治療法の比較，症例ごとの追跡調査，そして，多施設共同の大規模臨床研究が行われているが，その母集団は，共通の病理組織学的基盤のもとに進められるべきであろう。すなわち，共通の病変パラメータのもとにその定量性が表現され，それにより，腎生検の病理診断情報に互換性が生まれ，その結果，病理診断の標準化が可能となったとき，標準的な IgA 腎症治療指針作成のための EBM(科学的根拠に基づく医療 evidence based medicine)づくりが可能となる。今回の IgA 腎症に関する組織学的重症度分類(案)が旧分類に代わり全国的に用いられることを期待する。

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