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ORIGINAL ARTICLE

Association of apoptosis inhibitor of macrophage (AIM) expression with urinary protein and kidney dysfunction

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Abstract

Background Apoptosis inhibitor of macrophage (AIM) expressed on macrophages prolongs inflammation by protecting macrophages from apoptosis. Most circulating AIM co-exists with immunoglobulin M (IgM). AIM's pathophysiological role in relation to IgM remains unclear. Here we evaluated the glomerular expression/deposition of AIM and IgM in the kidney using immunohistochemistry and its associations with clinical manifestations in 43 patients with biopsy-confirmed kidney diseases.

Methods Kidney biopsy tissue from all patients was immunostained for AIM and IgM. Staining patterns and percent stained areas within the glomeruli were determined. Cells expressing AIM were identified by co-staining with macrophage and endothelial cell surface markers. Correlations between staining results and clinical parameters were evaluated using univariate and multivariate analyses.

Results AIM was deposited in various areas, such as mesangial and capillary area. A part of AIM expression was localized to CD68-positive macrophages in the glomerulus. Amount of glomerular expression was positively correlated with urinary protein in patients with severe proteinuria (urinary protein $\geq$0.5 g/day) and kidney dysfunction [estimated glomerular filtration ratio (eGFR) $<$60 ml/min/1.73 m^2]. Urinary protein was higher in patients exhibiting overlapping glomerular expression of AIM and IgM. Annual eGFR decline rate negatively correlated with AIM-positive area. AIM-positive area and initial serum creatinine were independently associated with decreased kidney function.

Conclusion AIM expression in the kidney was associated with urinary protein and decline in kidney function. Co-expression with IgM appeared to exacerbate AIM's deleterious effects on kidney function. Combined glomerular AIM and IgM expression is a candidate prognostic index for kidney disease.

Keywords Apoptosis inhibitor of macrophage (AIM) · Kidney disease · IgM

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Introduction

Apoptosis inhibitor of macrophage (AIM), a secreted protein of the scavenger receptor cysteine-rich superfamily, contributes to the pathogenesis of multiple diseases, including atherosclerosis, metabolic syndrome, and hepatic fibrosis [1–3], by protecting macrophages from apoptosis, resulting in prolonged inflammation [4, 5]. Upregulated AIM promoted hyperlipidemic atherosclerosis by suppressing foam cell apoptosis in a mouse model [6]. AIM

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was also associated with the progression of metabolic syndrome, including obesity and insulin resistance [7, 8].

Most circulating AIM is bound to immunoglobulin M (IgM) pentamers via Fc regions. Binding to IgM prevents AIM excretion in urine, thereby sustaining circulating AIM concentrations. In an obesity model, this AIM–IgM complex regulated the immune reaction of dendritic cells, resulting in autoantibody production [9, 10]. Glomerular IgM deposition occurs in numerous kidney diseases. Such deposition has been reported to activate C3, leading to focal segmental glomerulosclerosis in mice [11]. Another study found that glomerular IgM deposition contributed to the progression of non-sclerotic glomerular disease [12]. IgM nephropathy in humans is an idiopathic glomerulonephritis characterized by mesangial cell proliferation accompanied by prominent IgM deposition within mesangium lesions [13]. These reports indicate that IgM deposition may accelerate glomerular injury. However, the precise mechanisms remain unclear.

We speculated that glomerular AIM expression and IgM deposition may synergistically act to accelerate the progression of kidney disease. To explore this possibility, we investigated the expression of AIM and IgM in kidney glomeruli using immunohistochemistry and evaluated the correlation between the levels of expression/deposition and clinical manifestations.

Materials and methods

Patients

Forty-three patients with biopsy-confirmed kidney diseases were analyzed in this retrospective study. Ultrasound-guided kidney biopsy was performed between August 2011 and November 2012 at Kanazawa University Hospital. In fact, there were 60 patients with biopsy-proven kidney diseases in total during this period and 17 patients were excluded because of poor quality of immunohistochemical staining. Basal laboratory data were obtained at the same time as kidney biopsy tissue. Informed consent was obtained from all patients. This study was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committees of Kanazawa University Hospital (approval number: 1087).

Immunohistochemical staining

For immunohistochemistry, kidney biopsy tissues were frozen in Tissue-Tek O.C.T. compound (Sakura Finetek Co., Ltd., Tokyo) and cut into 2-μm-thick sections. The tissue sections were stained using an indirect method to assess AIM, IgM, CD68, and CD31 immunoexpression levels. Briefly, sections were immersed in phosphate-buffered saline (PBS) for 15 min and digested by proteinase K (S3020, Dako, Tokyo) at room temperature for 10 min. To reduce non-specific staining, the sections were incubated with Protein Block Serum Free (X0909, Dako) at room temperature for 10 min, and the blocking solution was drained off. Blocked sections were then treated with primary antibody diluted in PBS. To detect glomerular AIM, sections were incubated with rabbit anti-AIM antibody (1:50, SA-3, B0520, Rab2, donated by Prof. T. Miyazaki) at 4 °C overnight and then with cyanine dye 3 (Cy3)-conjugated anti-rabbit immunoglobulin G (IgG) antibody (1:100, 711-166-152, Jackson ImmunoResearch, West Grove, PA) at room temperature for 1 h. For immunostaining of macrophages or endothelial cells, kidney sections were incubated with mouse anti-CD68 antibody (1:50, M0814, Dako) or mouse anti-CD31 antibody (1:50, M0823, Dako) at room temperature for 1 h, respectively, followed by staining with FITC-labeled anti-mouse IgG antibody (F0315, Dako) at 37 °C for 30 min. To detect IgM deposition, the sections were treated with FITC-labeled anti-human IgM antibody (1:5, F0317, Dako) at 37 °C for 30 min. The sections were then washed in PBS for 30 min.

Image analysis

For semiquantitative estimation of glomerular protein expression levels, images were digitized using Win Roof, Version 6.1 analysis software (Mitani Corp, Chiba). Each image was transformed into a 1360 × 1024-pixel matrix and viewed at ×200 magnification. We calculated the percent area of positive staining for AIM and IgM and the degree of spatial overlap (double positive) for all glomeruli in each specimen.

Statistical analysis

Results are expressed as mean ± standard deviation (SD). Correlations among clinical variables and staining results were evaluated by Pearson correlation coefficients. Student's t test and Mann–Whitney U tests were performed to compare values between groups as appropriate. Univariate and multivariate analyses were performed using Cox proportional hazards model to calculate hazard ratios (HRs) and 95 % confidence intervals (CIs). Multivariate analyses were performed by the backward stepwise approach. p values less than 0.05 were considered statistically significant. All statistical calculations were performed using IBM SPSS Statistics (Version 19, SPSS Inc., Chicago, IL).

Results

Patient characteristics

The baseline clinical parameters of all 43 patients are summarized in Table 1. The mean age was 53.1 years (range 23–81 years), mean blood urea nitrogen (BUN) was 22.2 mg/dl, mean serum creatinine (sCr) was 1.30 mg/dl, mean estimated glomerular filtration ratio (eGFR) was 62.3 ml/min/1.73 m^2, and mean urinary protein was 1.38 g/day. Nine patients were diagnosed with IgA nephropathy, six with rapidly progressive glomerulonephritis, and five with membranous nephropathy.

AIM- and IgM-positive areas in the glomerulus

We performed immunofluorescence staining of AIM and IgM in kidney biopsy specimens. The glomerular AIM- and IgM-positive areas showed five patterns: mainly overlapping, non-overlapping, both negative, only AIM positive, or only IgM positive (Fig. 1a–e). The particular pattern and percent positive areas of AIM and IgM immunoreactivity appeared unrelated to the specific kidney disease (data not shown).

Co-expression of glomerular AIM with cell surface markers

To determine the source of AIM, tissue samples were co-stained with anti-AIM and antibodies against the macrophage surface marker CD68 and endothelial cell marker CD31. The part of AIM-positive area overlapped with CD68-positive macrophages (Fig. 1f), whereas CD31-positive endothelial cells were not positive for AIM (Fig. 1g), indicating that AIM was expressed primarily or exclusively by macrophages at least in part within the glomeruli.

Associations between AIM/IgM expression levels and urinary protein

Next, we assessed the association between AIM expression/deposition and the laboratory indices of kidney dysfunction listed in Table 1. AIM staining area was positively correlated with urinary protein in patients with urinary protein excretion $\geq$0.5 g/day ($r = 0.64$, $p = 0.001$) (Fig. 2a), and urinary protein was higher in patients exhibiting overlapping staining for AIM and IgM (Fig. 2b). Moreover, in patients with low eGFR (<60 ml/min/1.73 m^2), univariate analysis revealed a mild positive correlation between AIM staining area and urinary protein

Table 1 Baseline characteristics of patients

Characteristic	Mean ± SD or number
Patients (number)	43
Age (years)	53.1 ± 16.5
Sex (male/female)	29/14
BUN (mg/dl)	22.2 ± 16.2
sCr (mg/dl)	1.30 ± 1.05
eGFR (ml/min/1.73 m^2)	62.3 ± 32.4
Urinary protein (g/day)	1.38 ± 1.55
Histopathological diagnosis	
IgA nephropathy	9
Rapidly progressive glomerulonephritis (MPO-ANCA/GBM associated)	6 (5/1)
Membranous nephropathy	5
Diabetic nephropathy	3
Minimal change nephrotic syndrome	3
Nephrosclerosis	3
Focal segmental glomerulosclerosis	3
Membranoproliferative glomerulonephritis	2
Lupus nephritis	2
Tubulointerstitial nephritis	2
Others	5

BUN blood urea nitrogen, *sCr* serum creatinine, *eGFR* estimated glomerular filtration ratio, *MPO-ANCA* myeloperoxidase-anti-neutrophil cytoplasmic antibody, *GBM* glomerular basement membrane

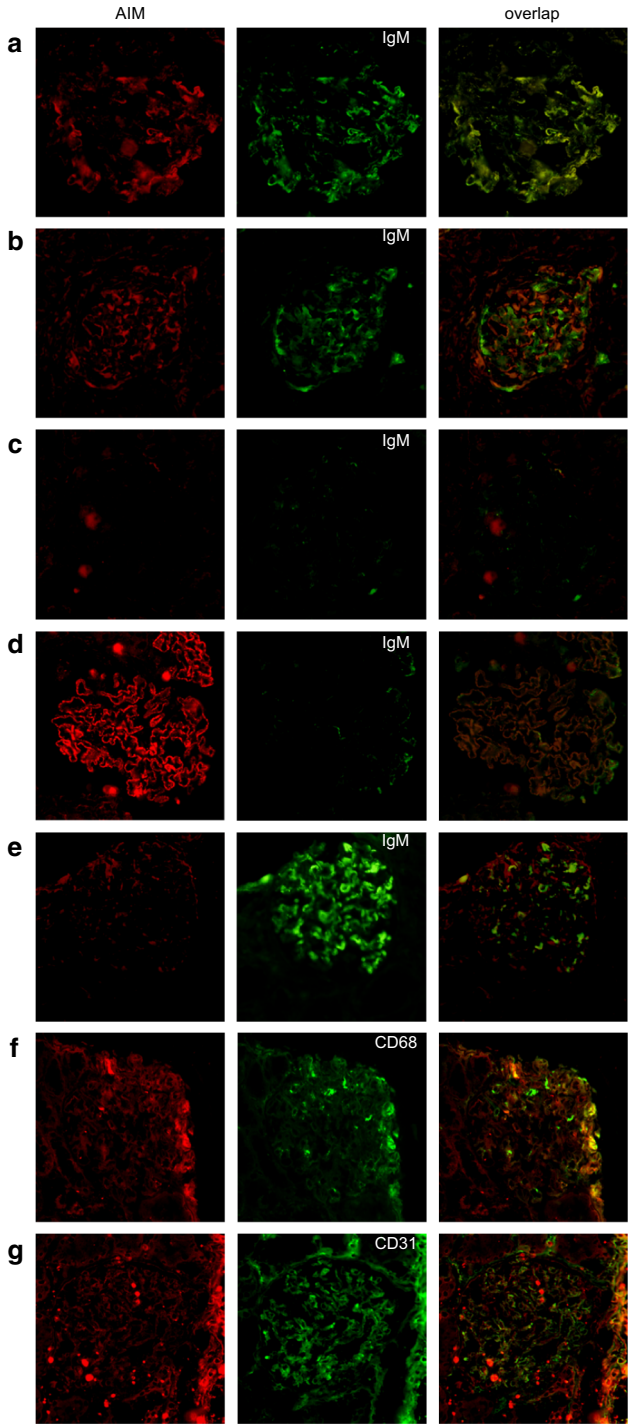

Fig. 1 The expression of AIM in diseased kidney. **a–e** Patterns of glomerular AIM and IgM immune expression. **a** Both AIM and IgM positive in similar areas (extensive overlap), **b** positive in different areas (non-overlap), **c** both negative, **d** only AIM positive, **e** only IgM positive. Cellular localization of AIM staining to CD68-positive macrophages (**f**) but not CD31-positive endothelial cells (**g**)

($r = 0.57$, $p = 0.004$) (Fig. 3a). Urinary protein also increased with the area of dual AIM plus IgM staining (Fig. 3b). In contrast, there was no correlation between AIM staining area and urinary protein in patients with normal or mild low eGFR ($\geq$60 ml/min/1.73 m^2).

Association between the deposition of AIM and kidney function

We then evaluated the relation between AIM and progression of kidney disease. Progressive disease was defined as initiation of dialysis, greater than 1.5-fold increase in sCr, or more than 50 % reduction in eGFR during the follow-up period. Four patients were excluded from the analysis because they were followed up at other hospitals soon after kidney biopsy and there were no data about progression of kidney disease in our hospital. The average follow-up period was 1.56 ± 1.23 years. Two patients started dialysis and three patients had more than 1.5-fold increase in sCr and/or more than 50 % reduction in eGFR. The AIM-positive area was significantly larger in these patients than in patients with no deterioration of kidney function (Table 2). The annual rate of eGFR decline was negatively correlated with AIM-positive area ($r = -0.41$, $p = 0.03$) (Fig. 4).

In univariate Cox regression analysis, AIM-positive area was significantly associated with decrease in kidney function (HR 1.24; 95 % CI 1.04–1.47; $p = 0.02$) (Table 3). In addition, dual AIM/IgM-positive area, urinary protein, initial sCr, and initial eGFR were also significantly related to decrease in kidney function. In contrast, IgM-positive area alone showed no correlation with kidney function. In multivariate analysis, including AIM-positive area, urinary protein, and initial sCr, decrease in kidney function was independently associated with AIM-positive area (HR 1.27; 95 % CI 1.00–1.60; $p = 0.04$) and initial sCr (HR 3.00; 95 % CI 1.20–7.50; $p = 0.02$) (Table 4).

Discussion

We investigated the expression of AIM in the kidney and association of glomerular AIM and IgM expression levels with clinical manifestations of kidney disease. Glomerular AIM deposition was associated with elevated urinary protein in patients with severe proteinuria (urinary protein $\geq$0.5 g/day) and more severe kidney dysfunction (eGFR $<$60 ml/min/1.73 m^2). Co-expression of IgM in the glomeruli further exacerbated proteinuria. Multivariate analysis revealed AIM deposition as an independent risk factor for declining kidney function during the follow-up period. These results strongly suggest that AIM deposition by infiltrating macrophages accelerates kidney injury in progressive kidney diseases and that this pathogenic effect is exacerbated by IgM deposition.

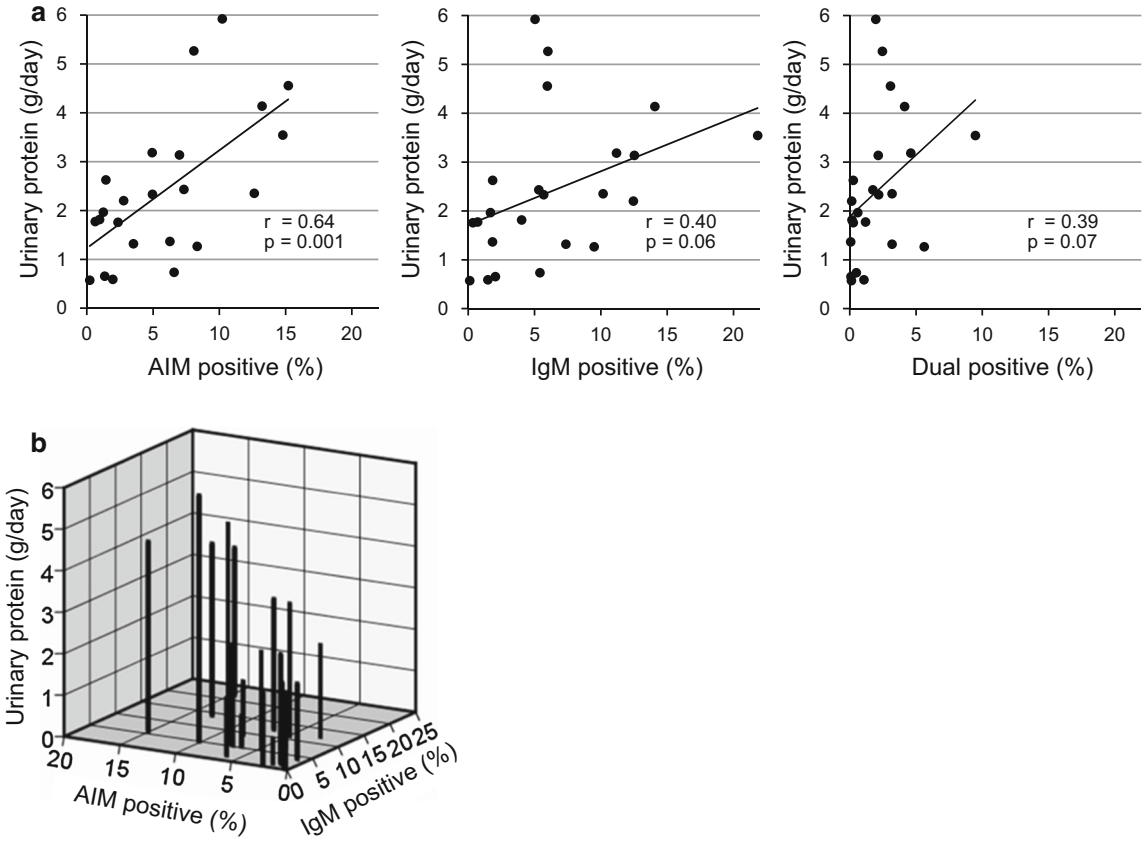

Fig. 2 The expression of AIM increased urinary protein in patients with proteinuria. Positive correlation between AIM-positive area and urinary protein in patients with urinary protein excretion ≥0.5 g/day (**a**). "Dual positive" is the overlap between AIM- and IgM-positive areas. Additional expression/deposition of IgM further enhanced urinary protein concentration (**a**, **b**)

Glomerular IgM deposition occurs in a variety of kidney diseases. IgM deposition in the glomerulus has been reported to activate C3, leading to focal segmental glomerulosclerosis in mice [11]. A recent study found that IgM deposition on injured glomerular capillaries caused complement-mediated glomerular injury. Moreover, the C2 IgM clone, but not the C5, induced albuminuria in a mouse model of glomerulonephritis [12]. Human studies have also reported that glomerular IgM deposition contributes to the pathogenesis of kidney diseases. IgM nephropathy is an idiopathic glomerulonephritis first described as a distinct entity in 1978 [14, 15]. It is characterized by mesangial proliferation accompanied by prominent IgM deposition within the mesangium lesion [13]. Clinical manifestations vary from nephritic syndrome [16] to kidney dysfunction [17]. These reports suggest that glomerular IgM deposition exacerbates the progression of kidney injury. Consistent with these findings, urinary protein increased with dual AIM plus IgM expression as measured by the percent area of overlapping immunoreactivity both in patients with high urinary secretion and patients with low eGFR. Thus, AIM and IgM appear to have synergistic deleterious effects on kidney function.

Macrophages contribute to the progression of kidney diseases, such as nephrosclerosis, diabetic nephropathy, and glomerulonephritis [18], by causing local inflammation. Infiltrating macrophages produce a variety of cytokines/chemokines that stimulate kidney resident immune cells, resulting in kidney damage [19–23]. Immunohistochemical staining revealed that AIM was deposited on various area such as mesangial area and capillary area. Among them, the part of AIM-positive area overlapped with CD68-positive macrophages, suggesting that this protein contributes to kidney injury by preventing macrophage apoptosis, thereby prolonging local inflammation at least in part. This may explain the worsening proteinuria at higher glomerular AIM expression levels. However, the precise mechanisms, including the contribution of IgM deposition to the pathophysiology of kidney disease, remain to be investigated.

The annual rate of eGFR decline was negatively correlated with AIM expression. Multivariate analysis also revealed glomerular AIM expression as a risk factor for progression of kidney dysfunction. Although IgM deposition alone was not associated with kidney dysfunction, the dual AIM/IgM-positive area was significantly associated

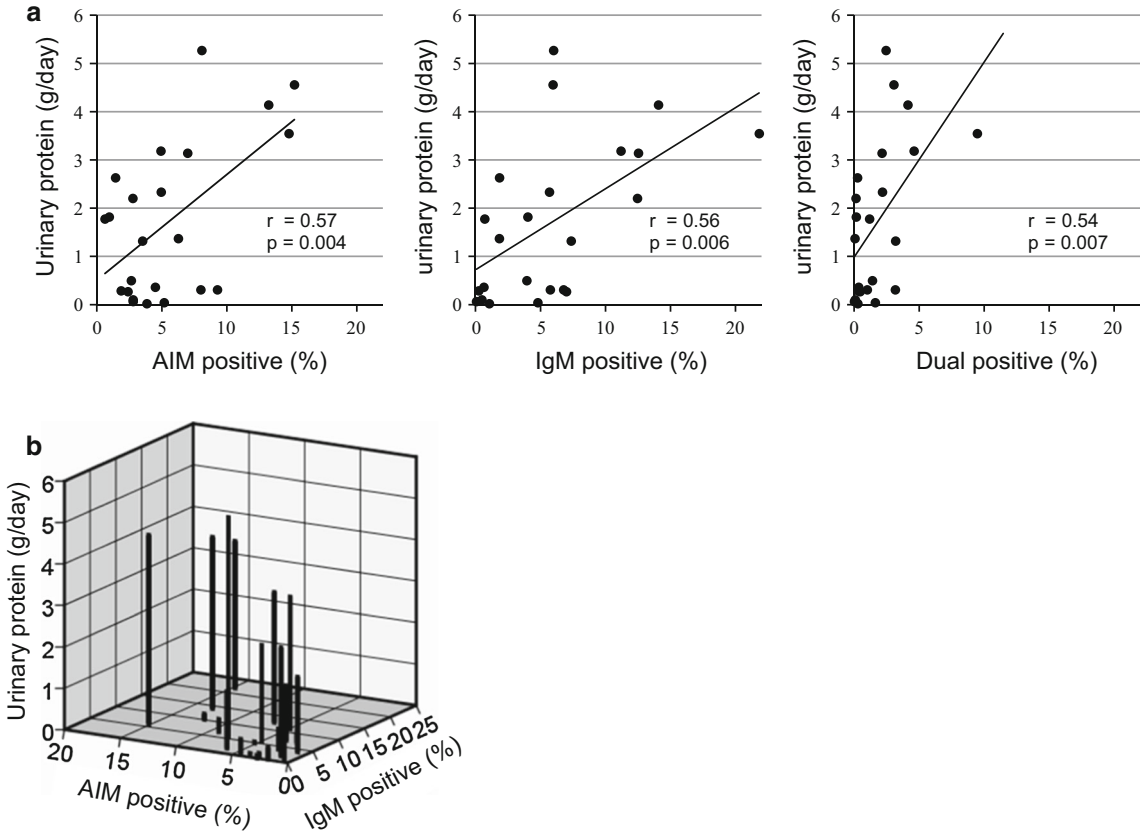

Fig. 3 The expression of AIM enhanced urinary protein in patients with low eGFR. AIM- and IgM-positive areas were positively correlated with urinary protein in patients with eGFR ≤60 ml/min/1.73 m^2 (**a**). "Dual positive" is the overlap between AIM- and IgM-positive areas. Urinary protein levels increased with the area of overlap (**a**, **b**)

Table 2 Comparison of the clinical characteristics of patients with and without decreased kidney function

	Patients with decreased kidney function	Patients without decreased kidney function	*p* value
Number (male/female)	5 (5/0)	34 (23/11)	
Age (years)	61.0 ± 22.6	50.5 ± 16.4	0.18
Follow-up period (years)	1.81 ± 1.18	1.53 ± 1.25	0.41
AIM-positive area (%)	10.7 ± 5.21*	5.10 ± 4.44	0.01
IgM-positive area (%)	12.3 ± 6.30*	4.40 ± 3.45	<0.001
Dual-positive area (%)	4.39 ± 2.92*	1.35 ± 1.57	<0.001
Initial sCr (mg/dl)	2.34 ± 1.40*	1.20 ± 0.97	0.03
Initial eGFR (ml/min/1.73 m^2)	31.3 ± 16.4*	66.5 ± 32.8	0.003
Initial urinary protein (g/day)	3.34 ± 1.25*	1.18 ± 1.46	0.003

'Decreased kidney function' is defined as initiation of dialysis, greater than 1.5-fold increase in sCr, or more than 50 % reduction in eGFR. 'Dual positive' is the overlap between AIM- and IgM-positive areas

* $p < 0.05$

with proteinuria and decreased eGFR. The HR of the dual-positive area was higher than that for the AIM-positive area, again consistent with a synergistic influence of IgM deposition on AIM-mediated progressive kidney disease.

There are several limitations to this study. The total number of patients did not permit analysis of specific kidney diseases and the follow-up period was short relative to the usual clinical course. In addition, several confounders, such as history of immunosuppressive drug use, were not considered.

In conclusion, our study demonstrates an association between glomerular AIM expression and higher urinary

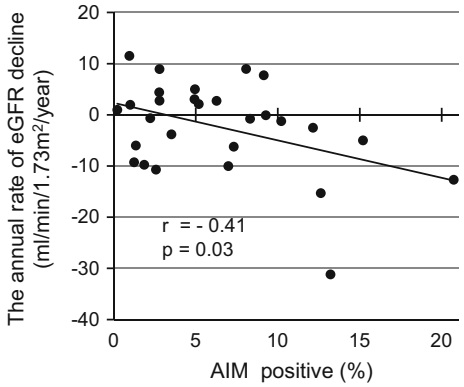

Fig. 4 The association between glomerular AIM expression and rate of decline in eGFR. AIM staining area was negatively correlated with the annual rate of eGFR decline

Table 3 Univariate analysis for factors associated with decreased kidney function

Factor	Hazard ratio (95 % CI)	*p* value
AIM-positive area (%)	1.24 (1.04–1.47)*	0.02
IgM-positive area (%)	3.29 (0.80–13.54)	0.10
Dual-positive area (%)	2.20 (1.27–3.83)*	0.005
Initial sCr (mg/dl)	2.07 (1.13–3.79)*	0.02
Initial eGFR (ml/min/1.73 m^2)	0.94 (0.88–1.00)*	0.04
Initial urinary protein (g/day)	1.57 (1.03–2.41)*	0.04

'Dual positive' is the overlap between AIM- and IgM-positive areas

95 % CI 95 % confidence interval

* $p < 0.05$

Table 4 Multivariate analysis for factors associated with decreased kidney function

Factor	Hazard ratio (95 % CI)	*p* value
AIM-positive area (%)	1.27 (1.00–1.60)*	0.04
Initial sCr (mg/dl)	3.00 (1.20–7.50)*	0.02
Initial urinary protein (g/day)	1.32 (0.74–2.38)	0.35

95 % CI 95 % confidence interval

* $p < 0.05$

protein in patients with severe proteinuria (urinary protein $\geq$0.5 g/day) and kidney dysfunction (eGFR <60 ml/min/1.73 m^2). Urinary protein was further increased by IgM deposition (greater area of overlapping AIM and IgM immunoreactivity). Further, AIM expression was an independent predictor of decline in kidney function. Glomerular AIM and IgM are candidate prognostic factors for worsening kidney disease.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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