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C3d deposition in the media of renal arterioles is a useful marker for arteriolosclerosis in IgA nephropathy

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ABSTRACT

C3d deposition in peritubular capillaries has been demonstrated to indicate antibody-mediated alloresponse during renal transplantation. C3d deposition in renal arterioles in IgA nephropathy (IgAN), however, is poorly documented. Especially, its significance to the pathology of primary glomerulonephritis remains unclear. This retrospective study included 340 patients with IgAN who underwent renal biopsy at our center. C3d strongly positive deposition in arterioles was observed in 123 (36.2%) of the 340 cases, and weakly positive deposition of C3d was observed in 217 cases (63.8%). In the weakly positive group, C3d mainly deposited in the intima of arterioles. In the strongly positive group, C3d deposited in the intima and the media of arterioles, presenting as the medial thickening and sclerosis of varying severities. The prognosis was worse in the C3d strongly positive group than in the weakly positive group during a 2-year follow-up ($P = .027$). The predictive value of C3d deposition in the media of arterioles in patients with IgAN may be a useful marker for arteriolosclerosis indicating unfavorable clinical outcomes.

1. Introduction

IgA nephropathy (IgAN) is a type of primary glomerulonephritis commonly observed in clinical patients, and it is also the most important cause of terminal renal failure. Histologic features such as glomerulosclerosis, mesangial hypercellularity, and interstitial fibrosis, and so on, are identified as independent predictors of renal failure. It is important to identify other risk factors associated with a poor progression of disease to better evaluate the prognostic significance of IgAN. The complement activation and expression could be an important risk factor in addition to histologic and clinical characteristics.

Some previous studies have shown that renal vascular lesion in IgAN is significantly associated with clinical parameters including blood pressure, urine protein, serum creatinine (SCr), and so on, and pathological features including glomerulosclerosis, interstitial fibrosis, mesangial hypercellularity, and so on. Prior studies showed that renal vascular lesion could be used as an important pathological prognostic indicator.[1–5] Other studies focus on the complement expression in the glomerular in patients with IgAN. Nakagawa H et al[6] found that the levels of glomerular C3d deposition in patients with IgAN were significantly higher than the levels observed in mesangial proliferative glomerulonephritis (MsPGN), suggesting that deposition of C3d in the mesangium may play an important role in chronic pathological effects observed in patients, and glomerular C3d deposition may be a useful marker for the degree of inflammatory activity in IgAN. In addition, the study by Gherghiceanu et al[7] had shown that C3d deposition in peritubular capillaries in IgAN is considered an indicator for unfavorable outcome.

C3d is an end-product of the 3 complement activation pathways. It is a stable marker that binds covalently to cell surfaces, and it is much easier to be detected in tissues. Presently, immunohistochemical staining of complement is universally considered as a useful diagnostic procedure in the assessment of renal biopsies, where C3d has shown to be a marker of humoral rejection. Although C3d may be potentially used for clinical analysis tool, the significance of C3d deposition in vessels, especially the sclerotic arterioles in IgAN, is not well documented. The purpose of the study was to assess the relationship between C3d deposition in arterioles and arteriolosclerosis in IgAN.

2. Materials and methods

2.1. Patient selection

The subjects in the present study consisted of 541 patients who received renal biopsy between January 2008 and November 2009 in our kidney treatment center. They included 340 patients with IgAN, 31 with MsPGN without IgA deposition, 33 with membranous nephropathy (MN), 26 with focal segmental glomerulosclerosis

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(FSGS), 35 with lupus nephritis (LN), 32 with diabetic nephropathy (DN), and 12 with hypertensive nephroslerosis (HN) as disease controls. These diagnoses were based on clinical findings and renal biopsies. Thirty-two cases of normal kidney (NK) from zero allograft biopsy tissue comprise the normal control group, and ethical considerations were followed.

2.2. Immunohistochemistry

Three-micrometer formaldehyde-fixed sections underwent immunohistochemical staining of C3d, IgG, IgM, IgA, C1q, fibrinogen (Fib), and complement receptor 2 (CD21). The details of the procedures were published previously.[8]

To assess the distribution of C3d deposition in arterioles, immunohistochemical double-label staining was performed. Smooth muscle actin (SMA) and C3d staining was accomplished by immersion in a 3% hydrogen peroxide solution for 10 minutes, incubation with anti-SMA antibodies at room temperature for 1 hour; treatment with a polymer enhancer at room temperature for 5 to 10 minutes, and a final treatment with an alkaline phosphatase-labeled secondary antibody incubated at room temperature for 20 minutes. Positive staining was then revealed by immersing the sections in an alkaline phosphatase chromogen substrate solution consisting of 5-bromo-4-chloro-3-indolyl phosphate and p-nitroblue tetrazolium chloride and then performed with C3d staining.

A semiquantitative grading of the intensity of C3d and other antibodies staining was performed. A score of 0 to 3 was defined as follows: 0, no staining (negative); 1, less than 25% of arterioles stained (+, weak); 2, 25% to 50% arterioles stained (2+, moderate); and 3, more than 50% arterioles stained (3+, strong).[9]

2.3. Pathological criteria

Microscopic observation of the pathological features (mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, tubular atrophy/interstitial fibrosis) of tissue samples from 340 patients with IgAN was performed according to the 2009 Oxford classification of IgAN system and Lee's pathological grades.[10,11] The diagnostic and scored criteria of arteriolosclerosis were based on the criteria by Katafuchi et al[12]: arteriole wall thickening was semiquantitatively estimated based on the cross-sectional ratio of luminal diameter to outer diameter. *Thickened arteriole wall* was defined as the ratio of less than 0.5 and no arteriole lesions in any arterial cross sections throughout the specimen. A *score of 1* was defined as arteriole lesions involving 1% to 25% of the arteriole cross sections; a *score of 2*, arteriole cross sections lesions involving 26% to 50%; and *a score of 3*, arteriole cross sections lesions involving more than 50%.

2.4. Clinical data

The study was conducted using retrospective data, with each patient's clinical data collected at the time of renal biopsy. Only complete patient data sets were used. Patient's age, sex, hematuria, SCr, blood urea nitrogen (BUN), mean arterial pressure (MAP), and an amount of 24-hour urine protein were documented. This study was approved by the hospital ethics committee prior to clinical data retrieval and analysis.

2.5. Study end points

Sixty-two patients with IgAN having Lee's pathological grade of IV had 2-year follow-up. The end point was the development of end-stage renal disease (ESRD) including the initiation of chronic dialysis or renal transplantation.[13]

2.6. Statistical analysis

Independent-sample tests or univariate data analysis of variance was used to compare different groups. Values were expressed as mean ± SD. A level of $P < .05$ was accepted as statistically significant. One-way analysis of variance was performed to evaluate the impact of C3d staining on renal survival using the Kaplan-Meier analysis. Calculations were performed using SPSS statistical software version 16.0 (SPSS, Chicago, Illinois).

3. Results

Clinical characteristics of the patients at the time of renal biopsy in the IgAN and control groups are shown in Table 1.

3.1. Immunohistochemistry findings

C3d staining was strongly positive in arterioles in 123 (36.2%) of the total 340 IgAN patient tissue samples (score ≥ 2). A total of 217 cases (63.8%) expressed weakly positive results (score = 1), and C3d negative (score=0) was not found in all the cases. In the weakly positive group, C3d was deposited in the absence of significantly thickened intima (Fig. 1A). In the strongly positive group, C3d deposition was found in the intima and the interstitium between the smooth muscle cells in the media of the thickened and sclerotic arterioles, but was not found in the adventitia (Fig. 1B, C).

A total of 116 of the 340 cases exhibit interlobular arteries. They had no C3d deposition or weak and irregular deposition in interlobular arteries. In the C3d strongly positive group, 65 cases showed vasa recta, of which 16 (24.6%) of cases showed that C3d deposits were well distributed in the vasa recta (Fig. 1D), whereas 96 cases showed vasa recta in the weakly positive group, of which only 7 (7.3%) of cases exhibited that C3d deposits were well distributed in the vasa recta. The difference was statistically significant between the 2 groups ($P < .05$). In addition, 14 (4.1%) of the total 340 cases observed showed signs of IgM deposition, although IgG, IgA, C1q, and Fib were not observed.

C3d deposition was also found in arterioles in the control groups (MsPGN, MN, FSGS, LN) and the NK group. C3d expression patterns were similar to those of patients with IgAN, although these were a small number of C3d strongly positive cases (Fig. 1E). The intensity of C3d was

Table 1
Clinical characteristics of the patients at the time of renal biopsy in the IgAN and control groups

Clinical characteristics	IgAN (n = 340)	Control group (n = 169)					
		MsPGN (n = 31)	MN (n = 33)	FSGS (n = 26)	LN (n = 35)	DN (n = 32)	HN (n = 12)
Age (y)	32.08 ± 10.87	32.19 ± 14.77	45.50 ± 14.82	28.00 ± 14.72	27.17 ± 12.12	52.22 ± 10.17	44.7 ± 14.1
Sex, male (%)	46.8	58.1	51.5	57.7	8.6	68.8	41.7
MAP (mm Hg)	91.11 ± 12.17	88.52 ± 11.15	94.45 ± 10.00	94.11 ± 11.66	94.82 ± 15.05	104.57 ± 10.36	122.4 ± 25.0
Hematuria (%)	15.6	3.2	0	0	2.8	0	8.3
Proteinuria (g/d)	2.05 ± 2.39	2.90 ± 2.14	5.80 ± 3.15	3.15 ± 1.83	3.38 ± 3.92	4.48 ± 1.65	1.4 ± 1.2
SCr (μmol/L)	113.10 ± 73.14	76.30 ± 33.76	74.89 ± 26.42	91.13 ± 43.24	81.05 ± 36.93	116.18 ± 52.17	212.5 ± 158.2
BUN (mmol/L)	6.25 ± 3.71	5.75 ± 3.17	5.27 ± 1.59	6.38 ± 3.59	7.48 ± 3.99	7.18 ± 2.83	10.1 ± 4.2

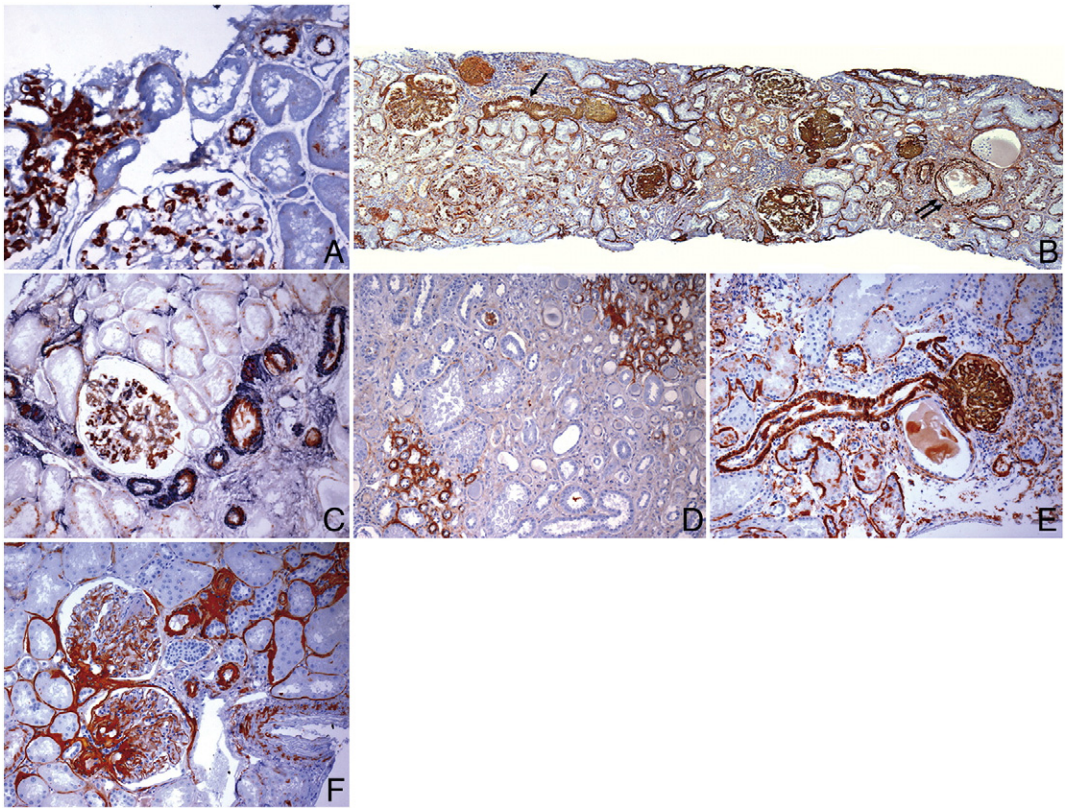

Fig. 1. (A) IgAN (Lee III). C3d weakly positive group. C3d deposited in the intima of arterioles; no C3d deposition in the media. Strong C3d deposition in the glomerular mesangium was also observed. (B) IgAN (Lee IV). C3d strongly positive group. C3d deposited in the intima and the interstitium between the smooth muscle cells in the media of sclerotic arterioles; no deposition in the adventitia (arrow), glomerular and sclerotic glomerular with strong C3d deposition, and interlobular artery with irregular and weak C3d deposition (double arrow). (C) IgAN (Lee IV). C3d strongly positive group. C3d (red) deposited in the intima and penetrated into the interstitium of the media; no deposition in the smooth muscle cells of the media (SMA, blue and black; double-label immunohistochemistry staining, SMA-C3d). (D) IgAN (Lee IV). C3d strongly positive group. Strong C3d deposited in vasa recta. (E) LN. C3d strongly deposited in the intima and media of afferent arteriole and in the glomerular capillary loops. (F) DN. Strong and uniform C3d deposition is shown in the intima of hyalinized arteriole and the afferent arteriole as well as in the glomerular mesangium, the capillary loops, and part of the tubular basement membrane. Weak and irregular C3d deposition is shown in the interlobular artery.

stronger than that of patients with IgAN ($P < .05$). In the DN and HN groups, however, the intensity of C3d was stronger than that in the IgAN group ($P < .05$; Table 2), and C3d was found to be uniformly deposited in the hyalinized arterioles with different deposition patterns occurring in IgAN and other nephropathy (Fig. 1F).

A small amount of IgM, IgG, IgA, and C1q deposition was observed in arterioles of tissue samples from the control groups; however, no obvious regularity was observed. In addition, Fib or CD21 deposition was not observed in each of these groups (Table 3).

3.2. C3d deposition in arterioles and patients with IgAN with different degrees of severity

According to the IgAN Lee's grade system, the intensity of C3d staining was significantly different in each grade (Spearman correlation coefficient of correlation = 0.223, $P = .000$), indicating that there exists a positive correlation between the intensity of C3d and the IgAN histologic classification (Table 4).

3.3. Histopathologic findings

The incidences of proliferative (M1), segmental sclerosis (S1), tubular atrophy/interstitial fibrosis (T1/2), and arteriolosclerosis were higher in the C3d strongly positive group than those observed in the C3d weakly positive group ($P < .05$). No significant difference in endocapillary proliferation (E1) was observed ($P > .05$; Table 5).

3.4. Clinical findings

Age, duration, SCr, and MAP at the time of biopsy were significantly higher in the C3d strongly positive group than in the weakly positive group ($P < .05$); however, there were no significant

Table 2
C3d deposition in different types of renal diseases and NK

Group	n	C3d
IgAN	340	1.48 ± 0.71*
NK	32	0.44 ± 0.50
MsPGN	31	0.81 ± 0.75
MN	33	0.58 ± 0.61
FSGS	26	0.77 ± 0.91
LN	35	0.54 ± 0.65
DN	32	2.53 ± 0.95
HN	12	2.25 ± 0.87

* $P < .05$ vs other renal diseases and NK.

Table 3
Other immune deposits in arterioles in different types of renal diseases and NK

Group	n	IgM	IgG	IgA	C1q	Fib
IgAN	340	0.08 ± 0.27	0	0	0	0
NK	32	0	0	0	0	0
MsPGN	31	0.45 ± 0.51	0.26 ± 0.45	0	0	0
MN	33	0.06 ± 0.24	0.12 ± 0.33	0	0	0
FSGS	26	0.19 ± 0.40	0.04 ± 0.20	0	0	0
LN	35	0.60 ± 0.50	0.43 ± 0.50	0.40 ± 0.50	0.49 ± 0.50	0
DN	32	0.56 ± 0.50	0.34 ± 0.48	0.12 ± 0.34	0	0
HN	12	0.08 ± 0.30	0.17 ± 0.40	0	0	0

Table 4
C3d deposition and patients with IgAN with different degrees of severity

Lee's pathological grades	n	C3d
I	7	0.57 ± 0.53
II	65	1.06 ± 0.75
III	76	1.21 ± 0.97
IV	181	1.44 ± 0.86
V	11	1.91 ± 0.94

differences in sex ratio, hematuria, 24-hour urine protein excretion, and BUN ($P > .05$) between the 2 groups (Table 6).

Treatment for 340 patients with IgAN was conducted according to published standards.[14] Of these, 62 patients were diagnosed as having IgAN Lee IV, including 33 cases that were strongly positive for C3d and 29 cases that were weakly positive for C3d. In the C3d strongly positive group, 5 cases evolved to ESRD during the follow-up. Renal survival at 2 years was 84.8% in the C3d strongly positive group vs 100% in the weakly positive group, in which no patient evolved to ESRD (log-rank, $P = .027$; Fig. 2).

4. Discussion

This study showed that the arterioles and arteries contained varying patterns and intensities of C3d deposition. Less than half (36.2%) of patients in the current study exhibited arterioles with C3d deposition in the intima and the interstitium between the smooth muscle cells in the media of thickened and sclerotic arterioles, and the smooth muscle cells lacked significant C3d expression, but almost no C3d deposited in the adventitia. More than half (63.8%) patients were weakly positive for C3d deposition. In addition, the C3d strongly positive group showed 24.6% of cases exhibiting uniform deposition of C3d in the vasa recta, whereas the weakly positive group showed only 7.3% of cases exhibiting C3d deposition in the vasa recta. These results suggest that C3d deposition is closely related to arteriolosclerosis and can extend to the vasa recta in patients with IgAN.

Arteriolosclerosis lesions are commonly morphologic characteristics in IgAN.[5,6,15] The present study used semiquantitative estimation of arteriole thickening and sclerosis, which was based on the cross-sectional ratio of luminal diameter to outer diameter. *Arterial-arteriolar wall thickening* was defined by a resultant ratio less than approximately 0.5. In fact, pathologists were able to perform diagnosis based on the above criteria, usually using subjective visual estimates as the primary determination. The use of strongly C3d deposition in arterioles to determine arteriole thickening and sclerosis provides a more accurate method with less visual subjectivity for diagnosis than the one only identified by usual staining, such as hematoxylin-eosin stain.

Precious study had shown that arteriosclerosis is common in patients with IgAN, in part, because immune complex deposition occurs in arterioles and arteries surrounding the glomerulus.[16] The results of our study showed that there was only a small amount of IgM deposition in arterioles in isolated cases. Moreover, C3d deposition in the arterioles of patients with IgAN was common, which lacks significant correlation between them. Therefore, we considered that C3d deposition in the arterioles has little correlation with immune deposits. There was no Fib expression, indicating that there is likely no relationship between C3d deposition in the arterioles and vasculitis.

To determine whether the C3d deposition in arterioles is associated with immune complex deposition or not, we chose some samples to make CD21 immunohistochemistry staining. As we know, CD21, an immune protein, mainly expressed in B cells and binds the C3d fragment of activated C3 that becomes covalently attached to targets of complement activation.[17] Our study showed that no CD21 expression was found in the NK or in various groups of glomerular disease, indicating that C3d deposition in the vessels does not belong to receptor-ligand binding mode.

C3d deposited in intima in early stage and then penetrates into the media of arterioles itself. The progress may be due to plasma proteins capable of penetrating blood vessel walls. C3d has a small molecular weight, allowing it to penetrate vessel walls under conditions of high blood pressure. C3d also has long half-life in vivo, which can be confirmed by analysis of C3d deposition in the sclerotic glomerular observed in IgAN. Therefore, permeability of plasma C3d may be the causative factor in high levels of C3d deposition in arterioles. Only a small amount of C3d deposition in the intima was observed in the normal control group. This may indicate that a small amount of plasma C3d can penetrate into the intima under the normal physiological state.

In the C3d strongly positive group, incidences of mesangial proliferative conditions (M1), segmental sclerosis (S1), and tubular atrophy/interstitial fibrosis (T1/2) were significantly higher than those found in the weakly positive group. In addition, a positive correlation was observed between the intensity of C3d staining and IgAN Lee's pathological grades. As Lee grade increments for patients

Table 5
C3d deposition and the histopathologic features of IgAN

Variables	C3d strongly positive group (n = 123)	C3d weakly positive group (n = 217)
Mesangial hypercellularity M1	96.7%*	88.5%
Segmental glomerulosclerosis S1	77.2%*	64.5%
Endocapillary hypercellularity E1	27.6%	30.0%
Tubular atrophy/interstitial fibrosis T1/2	44.7%*	30.9%
Arteriosclerosis score 3	8.9%*	0

* $P < .05$ vs C3d weakly positive group.

Table 6
C3d deposition and clinical characteristics of patients with IgAN

Variables	C3d strongly positive group (n = 123)	C3d weakly positive group (n = 217)
Age (y)	34.72 ± 11.11*	30.59 ± 10.46
Sex, male (%)	50.4	44.7
Duration (mo)	12.92 ± 9.38*	8.71 ± 9.64
MAP (mm Hg)	95.08 ± 15.39*	89.05 ± 9.52
Hematuria (%)	15.4	15.7
Proteinuria (g/24 h)	1.98 ± 3.00	2.08 ± 1.98
SCr (μmol/L)	138.07 ± 91.30*	96.84 ± 52.60
BUN (mmol/L)	6.67 ± 3.86	6.02 ± 3.61

* $P < .05$ vs C3d weakly positive group.

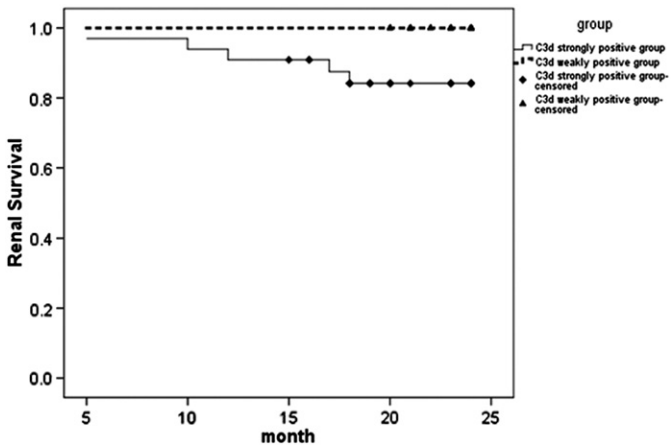

Fig. 2. Kaplan-Meier renal survival according to the C3d strongly positive group and C3d weakly positive group.

with IgAN increased, the intensity of C3d also progressively increased. These results suggest that C3d strongly positive deposition in arterioles is an effective prognostic indicator in patients with IgAN.

Patients with C3d strongly positive were observed to have increased levels of SCr and MAP compared with those from the weakly positive groups. Further follow-up studies revealed that the prognosis of the strongly positive group was significantly worse than that of the weakly positive group over a 2-year period. Therefore, this study indicates that strongly positive C3d deposition in arterioles is a useful marker for indicating risk in patients with IgAN. We concluded the main patterns and features of C3d deposition in arterioles and arteries with different degrees of thickening and sclerosis, as follows:

1. Interlobular arterial lesions were manifested as the intima thickening exceeding the media, characterized by the presence of irregular and a small number of C3d deposition in the intima and media.
2. Nonhyaline thickening and sclerotic arteriole lesions exhibited fibrous thickening of the intima and the media thickening due to the smooth muscle cell atrophy and interstitial cell hyperplasia. C3d and double-label C3d/SMA immunohistochemical staining demonstrated that this type is generally characterized by strong C3d deposition in the intima and the interstitium between the smooth muscle cells in the media of the sclerotic arterioles. This is the main type in patients with IgAN.
3. Arteriole hyalinization lesions were characterized by uniform C3d deposition in hyaline intima. It is relatively rare in patients with IgAN, but commonly in patients with benign hypertensive nephropathy and patients with DN.
4. Vasa recta uniform thickening lesions possess no obvious morphologies and rarely mentioned in the literature. The present study showed that C3d deposition in the vasa recta helps to show vasa recta lesions.

In summary, our study suggests that C3d deposition in the media of arterioles may be a useful marker for arteriosclerosis. C3d strongly positive deposition in arterioles was also found to be closely related to renal dysfunction and pathological changes. A 2-year follow-up study demonstrated that strong C3d deposition in arterioles is an indicator for poor prognosis, which can easily and effectively be used in clinic. C3d deposition in the arterioles indicates the poor prognosis in IgAN. Whether it is applied to other nephropathy remains to be determined.

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