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Original article

Ischemia-induced glomerular parietal epithelial cells hyperplasia: Commonly misdiagnosed cellular crescent in renal biopsy

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ABSTRACT

Ischemic pseudo-cellular crescent (IPCC) that is induced by ischemia and composed of hyperplastic glomerular parietal epithelial cells resembles cellular crescent. In this study, we aimed to assess the clinical and pathological features of IPCC in renal biopsy to avoid over-diagnosis and to determine the diagnostic basis. 4 IPCC cases diagnosed over a 4-year period (2012–2015) were evaluated for the study. Meanwhile, 5 cases of ANCA-associated glomerulonephritis and 5 cases of lupus nephritis (LN) were selected as control. Appropriate clinical data, morphology, and immunohistochemical features of all cases were retrieved. Results showed that the basement membrane of glomerulus with IPCC appeared as a concentric twisted ball, and glomerular cells of the lesion were reduced even entirely absent, and the adjacent afferent arterioles showed sclerosis or luminal stenosis. Furthermore, immune globulin deposition, vasculitis, and fibrinous exudate have not been observed in IPCC. While the cellular crescents showed diverse characteristics in both morphology and immunostaining in the control group. Therefore, these results indicated that IPCC is a sort of ischemic reactive hyperplasia and associated with sclerosis, stenosis, or obstruction of adjacent afferent arterioles, which is clearly different from cellular crescents result from glomerulonephritis.

1. Introduction

Occasionally, there are crescent-like structures within the Bowman's capsule that are composed of proliferating parietal epithelial cells which is induced by ischemia. They are frequently misdiagnosed as cellular crescents. Although cellular crescent often causes severe inflammatory reaction in the glomerulus in the form of extracapillary proliferative cellular lesion [1]. Such ischemic lesions are scarcely reported to date. We presume the cellular-crescent-like structure caused by ischemia as "ischemic pseudo-cellular crescent (IPCC) ". In this study, the clinical and pathological characteristics of 4 IPCC patients were retrospectively summarized to avoid overdiagnosis.

2. Materials and methods

Kidney biopsy reports from 10,736 cases were received from aound China from January 2012 to December 2015 and were analyzed. A total of 4 cases (0.37%) with an IPCC diagnosis were selected. The diagnostic criteria for IPCC in this study included the following: the number of proliferative glomerular parietal epithelial cells is at least up to 2 layers with at least half of the Bowman's capsule without inflammatory exudate; significantly shrunken basement membrane of the glomerulus; no characteristic glomerular nephritis with a lesion, such as focal segmental glomerulosclerosis (FSGS), immune complex deposits, or capillaritis. The corresponding afferent artery was significantly sclerotic. End-stagerenal disease (ESRD) was defined as start of dialysis or renal trans-plantation as the end point of the study [2,3]. 5 cases of ANCA-associated glomerulonephritis and 5 cases of lupus nephritis(LN) patients, who also exhibited a cellular crescent, were used as control samples. The study was approved by Dongfang hospital's Ethics and Research Committee.

The renal biopsies were examined by optical microscopy and immunohistochemistry(IHC). Sections for optical microscopy were stained with Haematoxylin and Eosin, Periodic acid–Schiff (PAS), Periodic acid-silver Methenamine and Masson's Trichrom (PAM-Masson) stains. Immunostaining for IgG, IgM, IgA, Fibrinogen, C3d, C4d and C1q were performed using the EliVisionTM system (Maixin Biocompany, Fuzhou China).A semiquantitative measurement of

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Table 1
Clinical and laboratory characteristics at presentation.

Patient no.	Age (years)	Sex	Clinical diagnosis	Urine protein (g/24 h)	Microscopic hematuria	SCr (umol/L)	BUN (mmol/L)	Hypertension	Follow up (months)	ESRD
1	42	M	Proteinuria of unknown origin	1.00	NA	74	5.33	No	52	NA
2	42	M	kidney transplant recipient	1.95	NA	475	27.92	Yes	31[a]	NA [a]
3	20	F	Proteinuria of unknown origin	3.14	NA	28	5.41	No	29	NA
4	24	M	Proteinuria of unknown origin	9.00	+++	63	3.76	No	18	NA

[a] The follow-up was performed after kidney transplantation.

Table 2
Pathological features of IPCC cases.

No.	Morphologic patterns	TIL	AAS	IPCC/Positive scores of corresponding glomerulus						
				IgG	IgM	IgA	C3d	C4d	C1q	Fib
1	IgA nephropathy (HS Lee Grade III)	1	2	0/0	0/0	0/0	0/3	0/0	0/0	0/0
2	Time-Zero Biopsy of donor kidney: glomerular minor lesion; Focal ischemic glomerulosclerosis	0	1	0/0	0/0	0/0	0/3	0/0	0/0	0/0
3	IgA nephropathy (HS Lee Grade II)	0	1	0/0	0/0	0/0	0/3	0/0	0/0	0/0
4	IgA nephropathy (HS Lee Grade II)	0	1	0/0	0/0	0/0	0/3	0/0	0/0	0/0

Table 3
Comparison of average score of immunohistochemistry grading between IPCC and control groups.

Group	*n*	IgG	IgM	IgA	C3d	C4d	C1q	Fib
[#]IPCC	4	0/0	0/0	0/0	0/3	0/0	0/0	0/0
[1]cellular crescents of ANCA – associated glomerulonephritis	5	0/0	0/0	0/0	0/3	0/1	0/1	3/1
[1]cellular crescents of LN	5	0/3	0/2	0/1	0/3	0/3	0/3	1/2

[#] IPCC/corresponding sclerous glomerulus.
[1] cellular crescent/esponding glomerulus.

the staining area was performed. The intensity of IHC staining was graded on a scale of 0 to 3+: 0, no staining (negative); 1, 1% to 25% of glomerulus stained (+, weak); 2, 25% to 50% glomerulus stained (++, moderate); 3, >50% glomerulus stained (+++, strong) [4,5].The average score of the group is the total scores/cases(the score is rounded).

2.1. Clinical data

The following information was collected: gender, age, clinical diagnosis and laboratory examination before renal biopsy, which included volume of proteinuria at 24 h, microscopic hematuria (<10 RBC/HPF+, 10–30 RBC/HPF ++, >30 RBC/HPF+++), serum creatinine (normal 53–124 μmol/L), blood urea nitrogen (BUN, normal 2.9–8.9 mmol/L), hypertension (systolic pressure ≥ 140 mmHg and or diastolic pressure ≥ 90 mmHg), and results from five hepatitis markers (HBsAg, HBeAg, HBsAb, HBeAb, and HBcAb).

2.2. Pathological criteria

Based on the Mayo ClinicRenal Pathology Society Consensus Report [6], The Oxford Classification of IgA Nephropathy [7], histopathologic classification of ANCA-associated glomerulonephritis [8], and reclassification of lupus glomerulonephritis [9,10], a score of 0–3 was applied to assess the afferent artery sclerosis (AAS): 0, no staining (negative); 1, 1–25% of afferent artery sclerosis (intima and/or media thickness of afferent artery, internal diameter/outer diameter <0.5); 26–50% afferent artery sclerosis; 3, >50% afferent artery sclerosis [11];2, an additional score was added with renal interlobar arterial and/or arcuate artery sclerosis [7]. For scoring renal tubulointerstitial lesions, the following characteristics were used: tubular atrophy/renal interstitial fibrosis ≤ 25% = 1, 26–50% = 2, >50% = 3 [7].

3. Results

3.1. Clinical features and laboratory characteristics (summarized in Table 1)

Age at diagnosis ranged from 20 to 42 years, and the group included 3 males and 1 female (M:F = 3:1). All patients had proteinuria in various degrees, and one of them had microscopic hematuria. Among them, a renal transplant patient had elevated BUN, serum creatinine, and hypertension, whose graft comes from donation after cardiac death (DCD) with no history of nephropathy.

3.2. Pathological features of IPCC cases (Tables 2 and 3, Figs. 1–4)

In IPCC lesions, the glomerular basement membrane appeared as a concentric twisted ball. The number of cells appeared reduced or even missing, and there were no lesions of protein deposition, vasculitis, or fibrinous exudate. The lesion had at least 2 layer of parietal epithelial cells hyperplasia, and ajacent afferent arteriole showed sclerosis or luminal stenosis. C3d expression was universally strong within the glomerular with IPCC. while positive staining of IgG, IgM, IgA, C4d, C1q, and Fib were not observed. All the immunostaining of proliferative parietal epithelial cells within the Bowman's Capsule were negative (Tables 2 and 3, Figs. 1 and 2). Conversely, Fib expression was identified in the cellular crescent of ANCA-associated glomerulonephritis, whereas immunostaining of IgG, IgM, IgA, C3d, C4d, and C1q were negative in it. Meanwhile C3d was strong positive, Fib expression was positive focal and segmentally, C4d and C1q expression intensities were weakly positive, and IgG, IgM, and IgA expressions were almost negative(Table 3, Fig. 3) in the glomerulus of ANCA-associated glomerulonephritis group. Then the cellular crescent of the LN shows little Fib deposition, and the same as IgG, IgM, IgA, C3d, C4d, and C1q, but there were varying degrees of expression of IgG, IgM, IgA, C3d, C4d, C1q, and Fib in the LN glomerulus(Table 3, Fig. 4).