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Waxy casts in the urinary sediment of patients with different types of glomerular diseases: Results of a prospective study

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ABSTRACT

Background: Casts are well known components of the urinary sediment. For most casts, the clinical associations are known and demonstrated, while for waxy casts they are totally unknown.
Methods: Prospective study for the search and count of waxy casts in the urinary sediment of patients with different types of glomerular diseases.
Results: Waxy casts were found in 39 out of 287 patients (13.6%), mostly in low number (1 to 9 out of 100 casts evaluated/sample). They were frequent in postinfectious glomerulonephritis and renal amyloidosis (5/9 patients, 44.5%, $p = 0.02$ for each condition), while they were rare in membranous nephropathy (4/67 patients, 6.0%, 0.04) and absent in focal segmental glomerulosclerosis (0/23 patients, $p = 0.05$). Waxy casts were associated significantly with higher serum creatinine levels ($p < 0.0001$), with the presence of >1 leukocyte/HPF, granular casts and leukocytic casts ($p = 0.001$ to 0.008) and with higher numbers of erythrocytes, leukocytes, renal tubular epithelial cells, granular casts, epithelial casts, and leukocytic casts ($p < 0.0001$ to $= 0.03$).
Conclusions: Waxy casts are uncommon and few in patients with glomerular diseases and are associated with impaired renal function and with several other structures of the urinary sediment.

1. Introduction

Urinary sediment examination is an integral part of urinalysis which, together with the evaluation of the physico–chemical parameters of the urine, is of paramount importance in the diagnosis of the diseases of the urinary tract [1]. Casts are well known components of the urinary sediment, whose classification includes: hyaline, granular (with fine or coarse granules), waxy, fatty, cellular (i.e., erythrocytic, leukocytic, and epithelial, which contain renal tubular epithelial cells [RTEC]), pigmented (i.e., hemoglobinic, myoglobinic, bilirubinic), containing microorganisms or crystals, and mixed (i.e., hyaline-granular, waxy-granular, waxy-cellular, etc.)[2,3].

While data on the frequency and/or clinical associations can be found in the literature about hyaline, hyaline-granular, granular, fatty, erythrocytic, leukocytic and epithelial casts [4–16], to our knowledge no information is available about waxy casts (WaC). This although they are structures which were already well known in the second half of the 19th century [17–19].

In this paper we report on the frequency and clinical association of WaC observed in the urinary sediment of a large cohort of patients with different types of glomerular diseases (GD), who were investigated prospectively.

2. Subjects and methods

The study was started in 1999 with the aim to investigate the global urinary sediment findings in patients with GD, the first results on 100 patients being published in 2005 [12]. The present study, focused only on WaC, is based on a larger and updated cohort of patients.

2.1. Inclusion and exclusion criteria

Patients were included in the study when fulfilled the two following inclusion criteria: (1) A clear-cut renal biopsy diagnosis of glomerular disease associated with moderate to very severe cylindruria (=1 cast every 4–7 low power fields [analytical sensitivity: 0.07 casts/uL, viewfield of the 10× ocular of our microscope being 18] to ≥1cast/low power field at 160×), defined according to Schreiner [20] with some modifications; and (2) Urine sediment examination performed a few hours before renal biopsy.

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We excluded patients with any evidence of urinary tract infection, leucorrhoea or bleeding from genital organs, menstruation, macroscopic hematuria or atypical features at renal biopsy (i.e. glomerular disease of uncertain classification).

2.2. Clinical features of patients

In addition to urine sediment findings, for each patient we recorded age, gender, plasma creatinine (μmol/L), urine pH and specific gravity (by URiSCAN, 10 SGL strip, YD Diagnostics, Korea) and urine protein excretion (g/L), measured by benzetonium chloride (health-associated upper reference limit ≤0.15 g/L). When it was possible, we also recorded the duration of disease, defined as the interval in months between the first laboratory findings indicating a renal disorder and the renal biopsy.

2.3. Urine sediment preparation and examination

To obtain a urine sample suitable for examination, patients were instructed to clean the external genitalia with soap and water, uncover the gland for male or spread the labia of the vagina for female and collect the second urine sample of the morning produced over 2 h after discarding the first part of micturition.

After collection, the urine samples for urine microscopy were handled in our laboratory according to the following standardized method, which was shown to provide reproducible inter sample quantitative results [21]: centrifugation for 10 min at 400 g of a 10 mL aliquot of urine transferred to a graduated glass tube with a conical bottom; removal by suction of 9.5 mL of supernatant urine; gentle but thorough resuspension of the pellet in the remaining 0.5 mL of urine; transfer by a precision pipette of 50 μL of urine to a glass slide; covering the sample with a 24 × 32 mm coverslip; urine sediment examination with a phase contrast Leitz Dialux 20 microscope (Leica Microsystems, GmbH, Wetzlar, Germany) within 3 h of urine collection.

For the first 3 years of the study, the samples were examined by a biologist who, in 2002, was replaced by another biologist, who is one of the authors of the present study (GG). Both of them had been instructed by one of us (GBF) and had the same criteria and capability for the identification of the particles, as demonstrated by periodical internal quality control schemes.

Each sample was first screened at low magnification (160×); in order to semiquantitate casts and thus to evaluate whether the patient could be included in the study. Then, for each sample, 100 casts were examined at high magnification (400×), which were classified as: hyaline, hyaline-granular, granular, WaC, fatty, erythrocytic, leukocytic and epithelial (= containing RTEC) casts. Thus, for each sample, the number of each cast subtype out of 100 casts evaluated was obtained.

WaC were identified on the basis of their distinguishing morphology, which is characterized by broken off or blunt ends, notched and sharp margins, lateral cracks, high refractive index and a surface whose appearance is reminiscent of that of melted wax (Fig. 1)[2,3].

A cast was defined as erythrocytic, leukocytic or epithelial even when only one erythrocyte, leukocyte or RTEC was evident within the cast matrix. When a cast contained more than one type of the above cells, it was classified according to the type of cell more prevalent in number.

Erythrocytes, leukocytes and RTECs were examined at high magnification (400×). They were quantified as the total number found over 20 high power fields (HPFs) as done in the previous study [21]. According to our reference values [12], microscopic hematuria and leukocyturia were defined as >1 erythrocyte or leukocyte/HPF, respectively. RTECs instead, due to their absence in normal urine, were recorded as present or absent and, when present, were also quantified as the total number counted over 20 HPFs. Lipid particles outside casts (appearing as droplets, either isolated or in aggregates or cholesterol crystals) were recorded only as present or absent.

For all samples we also evaluated both pH and specific gravity (SG). We did that because pH can influence the lysis of WBC [22] and the formation of casts [23], and SG because a value of <1.010 is associated with a possible lysis of erythrocytes and leukocytes [24].

Diagnoses of the various GD were based on the pathological reports, which for all cases were obtained by light and immunofluorescence investigation, while electron microscopy was performed only for selected cases. The light microscopy and immunufluorescent findings of renal biopsies were examined by two nephropathologists of the same team working on rotation, each diagnosis being reviewed and discussed with the attending nephrologist.

3. Statistical methods

Fisher's and Mann–Whitney test were used for categorical and continuous variables, respectively.

4. Results

From the beginning of February 1999 to the beginning of August 2012, 287 patients fulfilled the inclusion criteria and were enrolled into the study. Males were 162 and females 125, age ranged from 13 to 81 years (median, first and third quartile: 49.0, 37.0–63.0) and serum creatinine from 35 to 1140 μmol/L (97, 79–150). Proteinuria >150 mg/L was present in 278 patients (96.8%), ranging from 0.16 g to 23.1 g/L (2.1, 0.9–4.8). Urinary pH ranged from 5.0 to 8.0 (5.8, 5.4–6.0) and specific gravity from 1.005 to 1.030 (1.020, 1.015–1.025) (Table 1). The duration of renal disease, which we could retrieve for all 39 patients with WaC, and for 76 out of 248 patients without WaC (30.6%), ranged from 0.4 to 324 (5.0, 2.0–19.0) months. WaC were found in the urine of 39 patients (13.6%), while they were absent in the other 248 (86.4%). The two subgroups of patients, compared for the features described in Table 1, differed significantly only for serum creatinine, which was higher in patients with WaC (159, 88–388 vs 97, 79–132, $p < 0.0001$) (Table 1). Both pH and SG were similar in the two subgroups of patients, which rules out any influence by these two parameters on particle counts. The duration of the disease was also similar in the two subgroups of patients.

Overall, WaC were found in 39 patients (13.6%). In Table 2, we compared the relative frequency of patients with and without WaC for each disease, taking patients with other diseases as reference.

A statistically low frequency of WaC was found in idiopathic membranous nephropathy (with WaC: 4 patients, 6.0%) and focal segmental glomerulosclerosis (with WaC: no patients) and a statistically high frequency for WaC was found in acute postinfectious glomerulonephritis and amyloidosis (in both conditions, with WaC: 4, 44.5%) (Table 2).

The number of WaC/100 casts counted per sample ranged from 1 (23 samples, 59%) to 9 (1 sample, 2.6%) (median 1.0, 1.0–2.5). Table 3 shows the number WaC found in each disease. The 31 patients with 1 to 3 WaC/100 casts, compared to the 8 patients with 4 to 9 WaC/100 casts, had a median serum creatinine of 150 (88–335) vs 256 (167–503 μmol/L ($p = 0.19$) and a median proteinuria of 2.5 (1.1–5.2) vs 3.0 (1.6–5.6) g/L ($p = 0.74$).

We also investigated the association of WaC with the presence and number of the other particles of the urinary sediment (Table 4). WaC associated significantly with the presence of >1 leukocyte/HPF, granular casts and leukocytic casts. WaC also associated with higher numbers of erythrocytes, leukocytes, RTECs, granular casts, RTEC casts, and leukocytic casts, while they were significantly associated with lower number of hyaline casts.

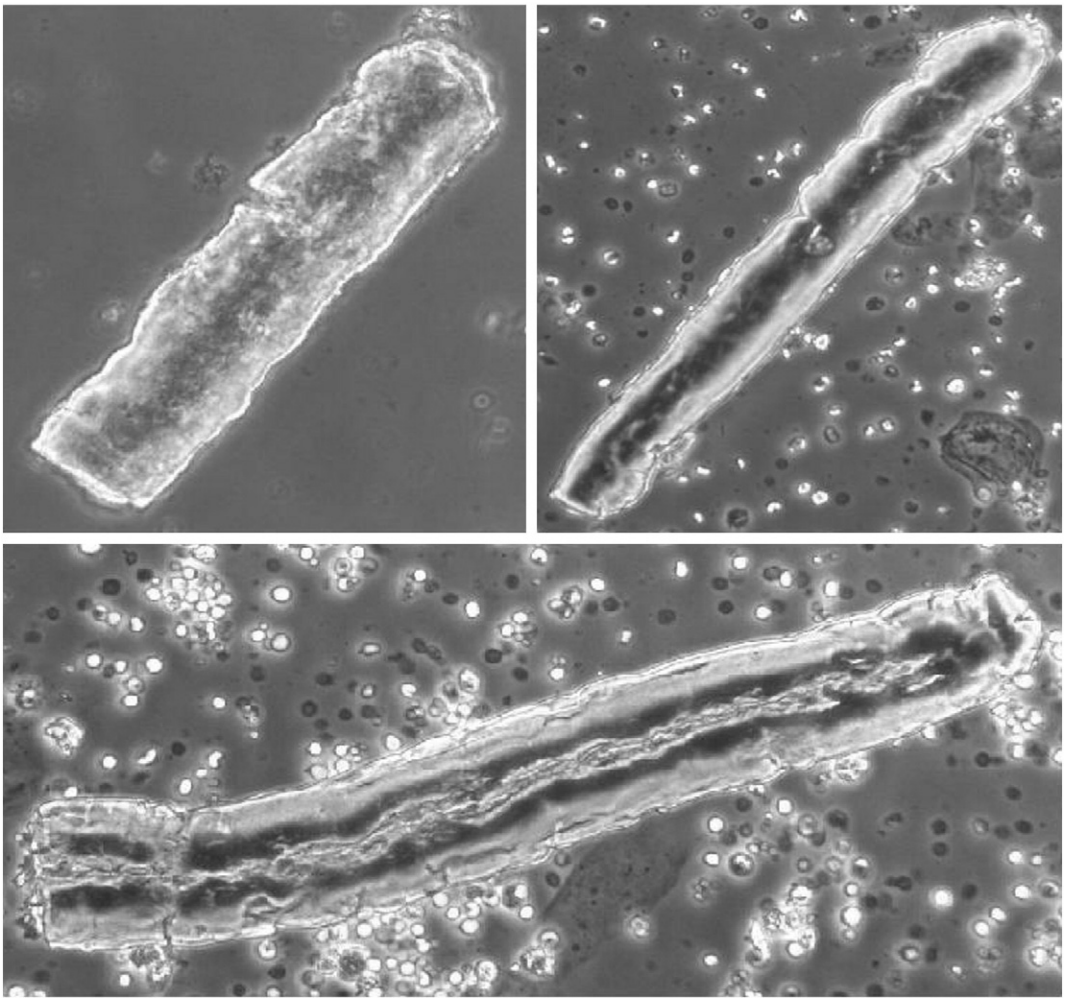

Fig. 1. Top left. A waxy cast with typical hard and indented edges (original size: 92.2 × 20.3 μm; original magnification: 400×). Top right. A waxy cast with indented edges and the typical "melted wax" appearance (original size: 541 × 66.5 μm; original magnification: 160×). Bottom. A big waxy cast with a deep crack along the whole length of the cast (original size: 816 × 115.4 μm, original magnification: 200×) (All images by phase contrast microscopy).

5. Discussion

Casts were well known components of the urinary sediment already in the second half of the 19th century [17–19], when their classification was very similar to that in use today [2,3]. Among casts there were, and still there are, WaC, which owe their name to their appearance, which is reminiscent of that of melted wax [2,3].

No information is available about the frequency of WaC in renal diseases. In fact, to the best of our knowledge, the clinical associations of WaC are described only in atlases or textbooks on urinary sediment [25–31], however without any sound evidence from literature. From these sources it appears that WaC would be associated with a wide spectrum of renal diseases, which would have in common the presence of acute kidney injury (AKI), rapidly progressive renal failure or chronic renal insufficiency.

This is in contrast with the available information about other types of casts. In fact, Imhof et al in 1976 [4] described a transient hyaline cylindruria after the administration of furosemide and etacrinic acid. Hebert et al in 1995 [8] found that casts containing erythrocytes and/or leukocytes were the most sensitive marker of a relapse of

Table 1
Clinical and urinary features of patients with and without WaC.

Feature	All patients (No = 287)	With waxy casts (No = 39)	Without waxy casts (No = 248)	p^*
M/F	162/125	21/18	141/107	0.73
Age (years)	49.0 (37.0–63.0)	48.0 (40.0–61.0)	49.0 (37.0–64.0)	0.90
S-creatinine (μmol/L)	97 (79–150)	159 (88–388)	97 (79–132)	<0.0001
Proteinuria > 0.15 g/L	278	38	240	0.60
Proteinuria (g/L)	2.1 (0.9–4.8)	2.6 (1.2–5.2)	1.9 (0.9–4.5)	0.15
Urinary pH	5.8 (5.4–6.0)	5.5 (5.4–6.0)	5.8 (5.4–6.2)	0.30
Urinary specific gravity	1.020 (1.015–1.025)	1.020 (1.014–1.020)	1.020 (1.015–1.025)	0.13
Duration of disease (months)	39/76	4.0 (2.0–11.0)	7.5 (1.5–24.0)	0.20
Patients with WaC/patients without WaC				

Age, S-creatinine, proteinuria (g/L), urinary pH and urinary specific gravity: median (1st and 3rd quartile).
* From Fisher's (categorical variables) or Mann–Whitney test (continuous variables).

Table 2
Glomerular diseases investigated and frequency of WaC.

Glomerular disease	Patients No.	With waxy casts no. (%)	Without waxy Casts no. (%)	p^*
Idiopathic membranous nephropathy	67	4 (6.0)	63 (94.0)	0.04
IgA nephropathy	57	9 (15.8)	48 (84.2)	0.36
SLE focal + diffuse proliferative GN	34	5 (14.7)	29 (85.3)	0.50
Extracapillary/necrotizing GN	31	6 (19.3)	25 (80.7)	0.40
Focal segmental glomerulosclerosis	23	0 (0.0)	23 (100)	0.05
Minimal change nephropathy	18	0 (0.0)	18 (100)	0.15
Mesangiocapillary GN	14	3 (21.4)	11 (78.6)	0.29
SLE proliferative + membranous GN	11	1 (9.1)	10 (90.9)	0.66
Acute postinfectious GN	9	4 (44.5)	5 (55.5)	0.02
Amyloidosis	9	4 (44.5)	5 (55.5)	0.02
Diabetic nephropathy	5	1 (20.0)	4 (80.0)	0.52
SLE membranous nephropathy	3	0 (0.0)	3 (100)	1.00
Schönlein-Henoch purpura GN	3	1 (33.3)	2 (66.7)	0.36
Others**	3	1 (33.3)	2 (66.7)	0.36
Total	287	39 (13.6)	248 (86.4)	

Abbreviations: GN = glomerulonephritis; SLE: systemic lupus erythematosus.
* From Fisher's test. ** Fibrillary GN, 1; Monoclonal IgG GN, 1, Alport syndrome GN, 1.

lupus nephritis. Ibsel et al in 1997 [9] reported on the poor prognostic significance of hyaline-granular casts in patients with IgA nephropathy. Vikse et al in 2002 [11] found that in mesangioproliferative glomerulonephritis granular casts were significantly associated with serum creatinine, serum albumin and proteinuria at presentation, with some histologic changes at renal biopsy and with a poor renal prognosis at follow-up. Fogazzi et al in 2005 [12], found higher frequency and numbers of erythrocytic and RTEC casts in proliferative GD compared with non proliferative GD, while fatty casts were more numerous in the latter group. Nakayama et al in 2008 [13] found that, in patients with IgA nephropathy, hyaline, granular, erythrocytic, leukocytic and fatty casts associated significantly with the histologic grading at renal biopsy and with a poor renal prognosis. Chawla et al in 2008 [14] found that patients who did not recover from AKI had a significantly higher "cast scoring index", based on the number of granular and RTEC casts, than patients who recovered renal function. Perazella et al in 2008 [15] found that a scoring index based on the number of granular casts and RTEC could distinguish AKI due to prerenal causes from acute tubular necrosis with a 76% sensitivity, 86% specificity and a positive likelihood ratio of 5.75. Fogazzi et al in 2012 [16] found erythrocytic casts in the urine of 6 out of 21 patients with acute interstitial nephritis from different causes (28.5%), a finding which was much higher than that reported in previous literature. Finally, various authors reported on erythrocytic casts in a wide spectrum of GD [5–7,10], with a prevalence which ranged from 22% [5] to 55 % [10].

No better known than the clinical associations is WaC composition. Since 1966 it is known that casts have a matrix which is made of Tamm-Horsfall glycoprotein (THg)[32], in which particles such as granules, cells, microorganisms or crystals can be trapped within the renal tubules during cast formation. The common view suggests that WaC would derive from the degeneration of other types of casts, especially granular casts, a process which would occur within the renal tubules [25–27,29–31]. However, no data can be found in the literature to support this view. The only study available on this subject is that by Haber and Lindner, published in 1977, who investigated by scanning electron microscopy the surface ultrastructure of different types of casts [33]. In that study, it was found that WaC had a slightly irregular surface, broken up into "plates" of unknown nature, which overlaid a fibrillar internal meshwork, similar to that of hyaline casts, and which was probably made of THg. This finding led the authors to state that WaC had "certain features of a basic hyaline cast origin with secondary alterations by products in the urine". This view, however, seems to be in contrast with the results of a study we performed in our laboratory several years ago, which was published only in abstract format [34]. Sixteen urinary sediments from 15 patients with either primary or secondary GD were stained with a polyclonal monospecific fluoresceinated sheep antihuman serum to THg and then examined by phase contrast microscopy coupled with immunofluorescence microscopy. A total number of 933 casts were investigated and while a ++ or +++ staining for THg was observed in all hyaline (No = 183), hyaline-granular (No = 113) and mixed casts (No = 53), THg was not found in any of 138 WaC. Thus, we believe that the composition of WaC is still largely unknown today.

Table 3
Number of waxy casts/100 casts counted in each sample (when present).

Disease (no. of patients with waxy casts)	Number of waxy casts/100 casts counted per sample								
	1	2	3	4	5	6	7	8	9
Idiopathic membranous nephropathy (4)	4								
IgA nephropathy (9)	3	3	1		2				
SLE focal + diffuse proliferative GN (5)	3					1			1
Extracapillary/necrotizing GN (6)	3	1		1			1		
Mesangiocapillary GN (3)	1	1		1					
SLE proliferative + membranous GN (1)	1								
Acute postinfectious GN (4)	3			1					
Amyloidosis (4)	2	1	1						
Diabetic nephropathy (1)	1								
Schönlein-Henoch purpura GN (1)	1								
Others (1) **	1								
TOTAL	23	6	2	3	2	1	1	0	1

GN = glomerulonephritis.
** = monoclonal IgG GN.

To the best of our knowledge, the present prospective study, which is based on a standardized and accurate methodology for the examination of urinary sediments and is done on a large cohort of patients with different types of GD, is the only one entirely focused on WaC.

Our study demonstrates that WaC were associated with higher levels of serum creatinine, while they were neither influenced by proteinuria nor by the duration of the disease (although this feature is known for only about 30% of patients without WaC). Our study also shows that WaC could be found in a wide spectrum of GD, but especially in acute postinfectious glomerulonephritis (GN) and in renal amyloidosis. This result is difficult to explain since renal amylodosis and acute postinfectious GN are very different diseases. In fact, amyloidosis is most often associated with monoclonal gammopathies, does not show inflammatory lesions at renal biopsy, develops slowly over time (median duration of disease in the 4 patients with WaC: 9.5 months, range 5 to 25 months), and is associated with either normal renal function or chronic renal insufficiency (median serum creatinine in the 4 patients with WaC: 119 μmol/L, range 79–327 μmol/L). On the contrary, acute postinfectious GN is an inflammatory disorder, which

Table 4
Frequency and number of urine sediment particles in patients with and without WaC.

Urine sediment particle		With waxy casts (No. 39)	Without waxy Casts (No. 248)	p^*
RBC (>1/HPF) RBC	Frequency (%)	35 (89%)	211 (85%)	0.62
	Number/20 HPF	410.0 (88.0–1091.0)	149.5 (42.5–460.5)	0.006
WBC (>1/HPF)	Frequency (%)	28 (71%)	107 (43%)	0.001
WBC	Number/20 HPF	46.0 (14.0–96.0)	16.5 (7.0–43.0)	0.002
RTECS	Frequency (%)	28 (71%)	138 (55%)	0.08
	Number/20 HPF	3.0 (0.0–10.0)	1.0 (0.0–4.0)	0.004
Hyaline casts	Frequency (%)	39 (100%)	245 (98%)	1.00
	Number/100 casts	12.0 (7.0–29.0)	28.0 (14.0–46.5)	0.0003
Hyaline-granular casts	Frequency (%)	39 (100%)	246 (99%)	1.00
	Number/100 casts	50.0 (34.0–64.0)	43.0 (32.0–55.0)	0.13
Granular casts	Frequency (%)	27 (69%)	97 (39%)	0.001
	Number/100 casts	3.0 (0.0–6.0)	0.0 (0.0–1.0)	<0.0001
Fatty casts	Frequency (%)	27 (69%)	177 (71%)	0.85
	Number/100 casts	3.0 (0.0–14.0)	6.0 (0.0–19.0)	0.38
RTEC casts	Frequency (%)	27 (69%)	130 (52%)	0.06
	Number/100 casts	2.0 (0.0–5.0)	1.0 (0.0–3.0)	0.03
Leukocytic casts	Frequency (%)	12 (30%)	35 (14%)	0.02
	Number/100 casts	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.008
Erythrocytic casts	Frequency (%)	27 (69%)	155 (62%)	0.48
	Number/100 casts	2.0 (0.0–7.0)	1.0 (0.0–4.5)	0.17
Lipids	Frequency (%)	24 (61%)	165 (66%)	0.86

Table shows number of patients for categorical variables or median (1st and 3rd quartile) for continuous variables.
*From Fisher's (categorical variables) or Mann–Whitney test (continuous variables).
Number of particles: median (1st and 3rd quartile).

develops in response to infectious agents, as demonstrated by the presence in the glomeruli of high numbers of polymorphonuclear leukocytes, and has a rapid course (median duration of diseases in the 4 patients with WaC: 1.5 months,range 0.5–3 months) with acutely impaired renal function (median serum creatinine in the 4 patients with WaC: 247 μmol/L, range 141–406 μmol/L).

Moreover, in our study, WaC were not found in conditions such as focal and segmental glomerulosclerosis and minimal change nephropathy and were rare in idiopathic membranous nephropathy. Interestingly, these three conditions have in common the lack of inflammatory lesions at renal biopsy, even though the pathogenetic mechanisms involved are very different.

In the majority of cases, we found that WaC were in small numbers, the samples with ≥4 WaC out of 100 casts evaluated representing only 1/5 of the samples with WaC. Finally, we found that WaC associate with the presence of leukocyturia, granular casts and leukocytic casts and with higher numbers of particles such as erythrocytes, leukocytes, RTECs, granular casts, RTEC casts, and leukocytic casts, while they are significantly associated with lower number of hyaline casts. We do not have any explanations for the negative association between WaC and hyaline casts. However, this finding might be an additional evidence against the view that WaC derive from hyaline casts, as suggested by Haber and Lindner [33].

Our results confirm the common belief that WaC are associated with renal insufficiency and that they can be found in various types of GD. This fact, however, does not elucidate the mechanisms of their formation and composition, which for the time being remains unknown.

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