Outcome of reclassification of World Health Organization (WHO) class III under International Society of Nephrology-Renal Pathology Society (ISN-RPS) classification: retrospective observational study

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Abstract The outcome of systemic lupus erythematosus (SLE) is largely influenced by the existence of lupus nephritis (LN), and its histologic classification guides the treatment and prognosis of SLE. International Society of Nephrology-Renal Pathology Society (ISN-RPS) announced a revised classification of LN in 2004. The present study investigated the differential outcome of World Health Organization (WHO) class III LN when reclassified according to ISN-RPS classification. Forty-three patients with biopsy-proven WHO class III LN at a single tertiary hospital were included in the study. Baseline characteristics at the time of renal biopsy and clinical data during follow-up were obtained from medical records. Renal response to treatment at one-year follow-up was analyzed in three ways; complete response (CR), partial response (PR), and no response (NR). Of 43 patients with previous WHO class III

LN, 12 cases were reclassified into ISN-RPS class IV (9 cases of class IV-S and 3 cases of IV-G). Baseline characteristics at the time of renal biopsy were not different between the reclassified class IV and remaining class III LN group except activity index on renal histology, which was significantly elevated in the reclassified class IV group (4.90 vs. 6.75; $P = 0.02$). Significantly higher number of patients with remaining class III LN achieved CR to treatment than those with reclassified class IV LN at one-year follow-up since initial biopsy (CR: PR: NR; 16:7:7 vs. 3:1:8; $P = 0.032$). Our study suggests that the ISN-RPS classification is more advantageous in predicting renal outcome and guiding treatment when evaluating previously classified WHO class III LN.

Keywords Systemic lupus erythematosus · Lupus nephritis · ISN-RPS classification · Class-switching event · Renal outcome

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Introduction

Renal involvement in systemic lupus erythematosus (SLE) occurs in up to 60% of cases during the disease course and is a major determinant of the outcome [1]. Since the publication of World Health Organization (WHO) classification of lupus nephritis (LN) [2–5], there have been numerous attempts in order to make better connection between the histologic findings and the renal prognosis. The evolution of the WHO classification, however, did not meet its need because of its rather vague definitions. In this vein, International Society of Nephrology-Renal Pathology Society (ISN-RPS) announced a revised classification of LN in 2004 [6]. Using this new classification system, many investigators have tried to compare the differential

outcome between class IV-S and IV-G LN, the newly added subcategories, with controversial results [7–11].

At this point, a noticeable finding is that class-switching events from WHO class III to ISN-RPS class IV were the most common class-switching events when the ISN-RPS classification was applied [12]. The presence of segmental endocapillary proliferation itself rather than the affected extent was used to define WHO class III LN. On the other hand, the ISN-RPS system allowed higher class allocation if more portions of glomerulus were involved. To our knowledge, little is known of the differential outcome of WHO class III LN when reclassified according to the ISN-RPS classification.

We conducted retrospective observational study to investigate the baseline characteristics and the renal response to treatment between the newly classified class IV LN according to the ISN-RPS classification and the remaining class III LN, both of which were previously WHO class III LN. In the present study, our data demonstrate that the ISN-RPS classification is more advantageous in predicting renal outcome when evaluating previously classified WHO class III LN.

Patients and methods

Patient selection

Biopsy specimens from cases diagnosed as LN were retrieved from pathology files of the Samsung Medical Center (Seoul, Korea) and reexamined by three pathologists using the ISN-RPS classification system. From January 1995 to February 2007, 48 patients with biopsy-proven WHO class III LN were identified. Among these, 43 patients were enrolled to study because a minimum of 10 glomeruli were required in the biopsy specimen to be eligible for the study in order to reasonably exclude a focal lesion according to the ISN-RPS classification. Forty-three specimens of these patients were included in the baseline analysis. Follow-up data for renal response and outcome were analyzed for 42 patients except one lost patient.

Data collection

The medical records were reviewed for the baseline characteristics at the time of renal biopsy such as clinical information and laboratory data including urinalysis. Pathologic indexes (subendothelial deposits on light microscope (LM) or electron microscope (EM), component of ISN-RPS class V, activity and chronicity index) were scored through the reexamination by pathologists. Clinical information and laboratory data were obtained every 6–12 months during the follow-up period. Treatment

regimen following the renal biopsy, change in proteinuria and the renal response to treatment at one-year follow-up, the cumulative dose of cyclophosphamide and prednisolone, the type of disease flare and the difference in the estimated glomerular filtration rate (Δ eGFR) and serum creatinine (Δ sCr) between the time of renal biopsy and the subsequent follow-up visit were obtained as the measure of clinical outcome.

Definitions

Renal response at the first year follow-up was divided into 3 groups; complete response (CR), partial response (PR), and no response (NR). Each group was defined as following; CR, a serum creatinine (sCr) < 1.4 mg/dl, urine protein <500 mg/day or trace by dipstick and the absence of active urinary sediment (≤ 10 red blood cell (RBC)/high power field (HPF)) and no casts; PR, a sCr < 1.4 mg/dl and urinary protein decreased by 50% or more from baseline or 1+ to 2+ by dipstick; and NR, a deterioration of renal function exclusive of other causes (such as sepsis or nephrotoxic agents), or a reduction in urinary protein with failure to reach PR, or persistence of active urinary sediments (>10 RBC/HPF).

Renal flare was evaluated using nephritic and proteinuric aspect except NR group at the first year follow-up; nephritic flare-up, an increase or recurrence of active urinary sediments (≥ 10 RBC/HPF) with or without a concomitant increase in urinary protein or sCr level; and proteinuric flare-up, an increase in urinary protein to more than 2 g/day after a CR, or a doubling of urinary protein in patients who achieved PR with or without a concomitant increase in sCr level.

Statistical analysis

Statistical analyses were performed using SPSS v.12.0.1 software. All values were expressed as mean $\pm$ standard deviation or percentage. Mann–Whitney U test was used for nonparametric analysis and Fisher's exact test for categorical data. *P* value of <0.05 was considered statistically significant.

Results

Baseline clinical characteristics

Of 43 patients, 12 (28%) were reclassified from WHO class III LN into ISN-RPS class IV. Thirty-one patients remained in class III. Of 12 reclassified ISN-RPS class IV LN from WHO class III LN, 9 were class IV-S LN and 3 were class IV-G LN (Fig. 1). Baseline characteristics of

each group at the time of renal biopsy are illustrated in Table 1. Female was predominant in both groups. In the reclassified ISN-RPS class IV, the time between the diagnosis of SLE and renal biopsy was shorter ($P = 0.06$). Lower serum albumin and complements and higher urinary protein level were also observed in this group, although these did not reach statistical significance. Renal function at the time of biopsy was well preserved in both groups. At the time of renal biopsy, asymptomatic urinary abnormalities were the most common condition followed by nephrotic syndrome in both groups ($P = 0.11$).

Initial pathologic parameters

The initial pathologic parameters of biopsy specimens are shown in Table 2. Activity index was significantly higher in the group with reclassified ISN-RPS class IV than the group that remained in class III ($P = 0.02$). Chronicity index was not different between two groups. Subendothelial deposits on LM and/or EM appeared in 14 (45.2%) patients with ISN-RPS class III and 8 (66.7%) in ISN-RPS class IV. Both groups had similar portion of combined class V component (51.6% vs. 54.5%).

Renal response to treatment and follow-up data during the first year after renal biopsy

Of 12 patients with reclassified ISN-RPS class IV LN, only 25% of patients achieved CR after 1 year of treatment. However, 53.3% patients who remained in class III LN achieved CR. Moreover, 67% of patients with reclassified ISN-RPS class IV LN were nonresponders, but only 23%

of patients who remained in class III LN remained nonresponsive. These results reached statistical significance (Table 3, $P = 0.032$). Among nonresponders in class III LN, 5 of 7 patients had deterioration of renal function without reduction of proteinuria while 5 of 8 nonresponders in class IV had dominant renal deterioration. This was too small to analyze statistically. Class V component of the initial pathology under ISN-RPS classification did not contribute to the renal response at each group of class III and class IV LN (data not shown). Among 9 patients with reclassified ISN-RPS class IV-S LN, 2 CR, 1 PR, and 6 NR were achieved. On the other hand, in 3 cases with reclassified class IV-G LN, 1 CR and 2 NR were noted.

Medical records were unavailable for review in one patient with reclassified ISN-RPS class III LN. Treatment regimen in 42 patients during the first year after renal biopsy was assessed. Prednisolone was prescribed in all patients either by itself ($N = 16$) or with other immunosuppressive agent ($N = 26$). Of 30 patients with ISN-RPS class III LN, 60% of patients received immunosuppressive agents after renal biopsy (13 cyclophosphamide, 2 mycophenolate mofetil, 2 azathioprine, and one cyclosporine). Sixty-seven percent of patients with ISN-RPS class IV LN received immunosuppressive agents (3 cyclophosphamide, 3 mycophenolated mofetil, one azathioprine, and one cyclosporine). The treatment modalities used in both groups of reclassified class IV and class III LN were not statistically different ($P = 0.74$). In terms of renal response when cyclophosphamide was used, there were 1 CR and 2 NR among 3 patients in ISN-RPS class IV (Table 4), whereas 8 CR, 4 PR, and 1 NR were observed among 13 patients in ISN-RPS class III. Table 4 shows individual treatment data of twelve patients with ISN-RPS class IV LN in detail.

Twelve patients (52.1%) in the reclassified ISN-RPS class III achieved >50% decrease in urinary protein after 1 year of treatment, while 2 patients (22.2%) in the reclassified ISN-RPS class IV achieved the same level of improvement ($P = 0.37$). The sCr remained almost unchanged in both groups (Δ sCr = -0.04 ± 0.24 vs. -0.07 ± 0.40 ; $P = 0.43$). Estimated glomerular filtration rate (eGFR), on the other hand, improved much more in the reclassified ISN-RPS class III than in the reclassified ISN-RPS class IV (Δ eGFR = 5.63 ± 31.91 vs. -12.92 ± 27.42 ; $P = 0.12$).

Follow-up data during total follow-up period

Mean follow-up duration was not different between the groups (72 ± 40 months in ISN-RPS class III vs. 80 ± 32 months in ISN-RPS class IV; $P = 0.45$). Twelve (40%) clinical flares were observed in the reclassified group of ISN-RPS class III and 3 (25%) flares in the reclassified ISN-RPS class IV group, but the type of flares was

Fig. 1 Study design and the renal response to treatment at one-year follow-up. ^aSpecimens with more than 10 glomeruli were enrolled to study for the eligibility of applying the ISN-RPS classification. ^bOne patient did not visit the clinic after the initial renal biopsy. ^cRenal response to treatment at one-year follow-up was assessed in ISN-RPS class III LN and ISN-RPS class IV ($P = 0.032$). WHO World Health Organization, ISN-RPS International Society of Nephrology-Renal Pathology Society, LN lupus nephritis, CR complete response, PR partial response, NR no response

Table 1 Baseline characteristics in patients with reclassified ISN-RPS class III and IV LN

	ISN-RPS class III (<i>N</i> = 31) mean ± SD; <i>N</i> (%)	ISN-RPS class IV (<i>N</i> = 12) mean ± SD; <i>N</i> (%)	<i>P</i> value
Female	27 (87.1)	11 (91.7)	1.00
SLE onset age	27.5 ± 10.7	30.7 ± 11.0	0.58
SLE duration at renal biopsy (months)	20.9 ± 25.3	10.1 ± 21.0	0.06
Length of follow-up since renal biopsy (months)	72.8 ± 40.4	80.9 ± 32.0	0.36
Parameters at renal biopsy			
White blood cell/mm ³ [3,150–8,630]	5,337 ± 2,667	6,429 ± 2,451	0.19
Hemoglobin level, g/dl [11.2–14.8]	10.6 ± 1.4	10.3 ± 1.9	0.75
Platelet count, x100 ³ /ul [138–347]	200 ± 74	218 ± 66	0.51
Serum albumin, g/dl [3.5–5.2]	2.88 ± 0.78	2.53 ± 0.89	0.24
Serum creatinine, mg/dl [0.6–1.1]	0.81 ± 0.24	0.75 ± 0.27	0.31
Estimated GFR, ml/min/1.73 m ² [60–150]	104.4 ± 35.6	105.8 ± 29.3	0.59
Urine protein, g/day [0.4–0.15]	3.11 ± 3.20	4.79 ± 5.67	0.40
Urine RBC/HPF [0–2]	2.6 ± 1.5	2.8 ± 1.5	0.76
C3, mg/dl [90–180]	53.91 ± 24.18	47.34 ± 18.58	0.49
C4, mg/dl [10–40]	10.83 ± 6.91	9.38 ± 6.25	0.58
Anti-dsDNA, IU/ml [0–7.5]	428.93 ± 717.40	424.45 ± 476.53	0.51
ESR, mm/hr [0–27]	52.89 ± 38.37	49.00 ± 35.33	1.00
CRP, mg/dl [0–0.3]	3.11 ± 11.32	0.55 ± 0.77	0.44
Comorbidity			
Hypertension (HTN)	6 (19.4)	5 (41.7)	0.24
Other underlying diseases			
Rheumatologic disease ^a	3 (9.7)	1 (8.3)	0.42
Non-rheumatologic disease except HTN ^b	10 (32.3)	3 (25.0)	0.11
Both	2 (6.5)	3 (25.0)	
Clinical setting			
Acute glomerulonephritis	0	2 (16.7)	
Nephrotic syndrome	9 (29.0)	3 (25.0)	
Asymptomatic urinary abnormalities	22 (71.0)	7 (58.3)	

These patients had the same class III LN under WHO classification

GFR glomerular filtration rate

^a Sjogren's syndrome (*N* = 2), antiphospholipid syndrome (*N* = 2), mixed connective tissue disease, polymyositis, scleroderma, relapsing polychondritis, rheumatoid arthritis

^b Pulmonary tuberculosis (*N* = 4), hypothyroidism (*N* = 3), idiopathic thrombocytopenia (*N* = 2), bronchial asthma, cerebrovascular accident, chronic thyroiditis, colon cancer, common bile duct stone, congestive heart failure, nasopharyngeal lymphoma, osteoarthritis, osteomyelitis, ovarian cancer, tuberculous lymphadenitis

Table 2 Pathologic parameters of initial renal biopsy specimen under ISN-RPS classification

	ISN-RPS class III (<i>N</i> = 31) mean ± SD; <i>N</i> (%)	ISN-RPS class IV (<i>N</i> = 12) mean ± SD; <i>N</i> (%)	<i>P</i> value
Activity index	4.90 ± 2.14	6.75 ± 2.18	0.02
Chronicity index	2.23 ± 1.54	2.83 ± 2.44	0.78
Subendothelial deposits on LM and/or EM	14 (45.2)	8 (66.7)	0.31
Combined class V component	16 (51.6)	6 (54.5)	1.00

LM light microscope, *EM* electron microscope

Table 3 Renal response to treatment and follow-up data during the first year after renal biopsy

	ISN-RPS class III (<i>N</i> = 30) mean $\pm$ SD; <i>N</i> (%)	ISN-RPS class IV (<i>N</i> = 12) mean $\pm$ SD; <i>N</i> (%)	<i>P</i> value
Cumulative dose during the first year since renal biopsy			
Cyclophosphamide, g	6.96 $\pm$ 1.36	6.59 $\pm$ 0.24	0.52
Prednisolone, g	4.73 $\pm$ 2.48	5.13 $\pm$ 2.56	0.73
Change of urinary protein at the first year follow-up visit			0.37
Same or increased proteinuria	7 (30.4)	3 (33.3)	
0 < decreased amount < 50%	4 (17.4)	4 (44.4)	
50% $\leq$ decreased amount < 75%	3 (13.0)	0	
Decreased amount $\geq$ 75%	9 (39.1)	2 (22.2)	
Renal response to treatment			0.032
CR	16 (53.3)	3 (25.0)	
PR	7 (23.3)	1 (8.3)	
NR	7 (23.3)	8 (66.7)	

CR complete response, PR partial response, NR no response

comparable. Chronic kidney disease of stage 3 or more developed in 4 (13.3%) in the reclassified group of ISN-RPS class III and 3 (25%) in the reclassified group of ISN-RPS class IV. One patient in each group required hemodialysis. End-stage renal disease (ESRD) in these patients had arisen early in the disease course (50 months in the ISN-RPS class III vs. 37 months in the ISN-RPS class IV). Excluding these patients, eGFR at the last follow-up visit was 100.38 ± 31.26 ml/min/1.73 m² in the reclassified ISN-RPS class III and 91.91 ± 32.80 ml/min/1.73 m² in the reclassified ISN-RPS class IV ($P = 0.41$). The sCr level at the time of last follow-up was 0.84 ± 0.45 mg/dl in ISN-RPS class III and 0.90 ± 0.48 mg/dl in ISN-RPS class IV ($P = 0.76$). There was a trend of lower eGFR and higher sCr in the reclassified class IV group, but did not reach statistical significance. A tendency of decreased renal function as measured by the absolute difference in eGFR was observed in the reclassified ISN-RPS class IV (Δ eGFR = 1.57 ± 39.83 in ISN-RPS class III vs. -18.42 ± 23.36 in ISN-RPS class IV; $P = 0.06$).

Discussion

The most commonly encountered reclassification event under the revised ISN-RPS classification criteria is from WHO class III to ISN-RPS class IV, and this is the first study to evaluate the differential outcome of patients with previous WHO class III LN when the new ISN-RPS classification is applied.

A previous study showed that the new ISN-RPS classification provided beneficial pathologic information relevant to the long-term renal outcome and the optimal therapy preventing ESRD and/or death in patients with LN

[10]. Our investigation, however, mainly focused on the class-switching events from previous WHO class III LN to ISN-RPS class IV LN and compared them with those which remained in class III under the ISN-RPS system. After applying the ISN-RPS classification system to 43 cases of WHO class III LN, 12 cases were reclassified to class IV LN, and 31 cases remained in class III LN. With regard to the interobserver variability among three pathologists, there were discrepancies in class designations as expected, but they were smaller under the ISN-RPS system compared to the WHO classification in overall (16.7% vs. 48%).

A significant finding was observed in that these two reclassified subsets of LN, which were originally classified as the same class III LN under the WHO system, exhibited distinguishable activity indexes on initial pathology and different renal responses and outcome. The reclassified class IV LN had higher activity index on initial biopsy, poorer renal response after 1 year of treatment and inferior renal outcome during total follow-up period. The fact that the reclassified class IV LN group showed higher activity index but not chronicity index is inconsistent with previous reports that suggested poor outcomes associated with the presence of chronic lesions [8, 13, 14]. A possible explanation is that the initial renal biopsy was performed in very early stage of disease process in our institution. Nevertheless, these data suggest that ISN-RPS classification is more advantageous in predicting the renal outcome of previously classified WHO class III LN and would provide better assistance in making therapeutic decision.

The poor renal response in the reclassified ISN-RPS class IV LN may have been caused by less frequent use of cyclophosphamide compared to reclassified ISN-RPS class

Table 4 Individual data of patients with ISN-RPS class IV LN

Patient number (<i>N</i> = 12)	IV-S or IV-G (S/G)	Cr (mg/dl)		eGFR (l/min/1.73 m ²)		Cumulative dose for 1 year after renal biopsy (g)			Renal response (CR/PR/NR) ^b	Flare up ^c
		At renal biopsy	1 year	At renal biopsy	1 year	CYC	Pd	Others ^a		
1	G	0.9	2.1	77	37	0	7.08	C: 33.20	NR	
2	S	0.6	0.8	108	77	0	4.32		CR	Y
3	S	0.62	0.68	123	103	0	4.02	A: 2.41	NR	
4	S	0.7	0.7	104	98	0	3.09		PR	
5	S	0.6	0.54	120	132	0	3.16	M: 612.00	NR	
6	S	0.6	0.9	113	67	0	6.86		NR	
7	G	1.5	0.9	43	73	6.70	4.32		CR	Y
8	S	0.6	0.58	134	133	0	2.97	M:126.50	NR	
9	S	0.9	0.8	71	76	6.31	3.12		NR	
10	G	0.52	0.71	144	100	0	5.20	M:155.52	NR	
11	S	0.6	0.7	130	109	6.75	11.88		NR	
12	S	0.9	1.1	99	74	0	5.60		CR	Y

CYC cyclophosphamide, Pd prednisolone, C cyclosporine, A azathioprine, M mycophenolate, CR complete response, PR partial response, NR no response, Y present

^a Other treatment modalities were used with prednisolone. Each number shown with capital letter represents other treatment modality with mean cumulative dose

^b Renal response was evaluated at 1 year of treatment after renal biopsy

^c Flare-up during total follow-up period was not assessed in NR group at 1 year

III LN. Although cyclophosphamide combined with glucocorticoid has been a standard induction therapy for WHO class IV LN as reported by the trials performed at the National Institutes of Health [15–18], there is no established optimal treatment for WHO class III LN. As expected, in the present study, individual patient of previously classified WHO class III LN was treated by various immunosuppressive agents on a case-by-case basis. It is important to note, however, that the use of immunosuppressive agents was more frequent in ISN-RPS class IV (8/12; 67%) compared to ISN-RPS class III (18/30; 60%). Moreover, the efficacy of cyclophosphamide was lower in ISN-RPS class IV (2 NR among 3 Total) compared to ISN-RPS class III (1 NR among 13 Total). Therefore, less frequent use of cyclophosphamide in ISN-RPS class IV may not be a sole contributor to the poor renal response. Although the sample size was too small to draw a conclusion, the new classification system may help identify the subgroup of patient that needs more aggressive therapy.

While much attention has been paid to the treatment response, renal outcome or prognostic factors of diffuse proliferative lupus nephritis, WHO class IV LN, in the past [19–23], scarce outcome and treatment response data are available for WHO class III LN. Therefore, our study is also significant in the fact that 43 cases of WHO class III LN were evaluated for the treatment responses and outcome. The renal outcome and treatment response of WHO class III LN appeared heterogeneous. After 1 year of

treatment, less than one half patients achieved CR, a fifth showed PR, and a third showed NR. These various outcome data imply the limitation of WHO classification system in terms of its usefulness in predicting the prognosis of WHO class III LN. Reclassification of WHO class III LN under the revised ISN-RPS classification revealed two different groups: ones that remained in class III and others that were reclassified to class IV. The newly classified class IV LN had poorer response compared to the remaining class III. Hence, the ISN-RPS criteria are more discriminative in predicting the outcome and exhibit better clinicopathologic correlation than WHO system.

Previously, three retrospective studies were performed to elucidate the distinction between class IV-S LN and IV-G LN under ISN-RPS classification. Of 33 patients with ISN-RPS class IV LN, 22 patients with class IV-G LN were compared to 11 patients with class IV-S LN [11]. Lower C4 level was observed in the IV-S group while sCr levels and diastolic blood pressures were significantly greater in the IV-G group. Histologically meaningful lesion was seen more frequently in the IV-S group. However, no significant difference was detected in outcomes in both groups, and thus, clinical and prognostic distinction between IV-S and IV-G remains to be proven. In a smaller Japanese group, 6 patients had the class IV-S LN, and 17 patients had the class IV-G LN [10]. IV-G group tended to have lower CH50 levels. In analysis of the 50% renal survival time, patients with class IV-S (95 months) LN

showed shorter mean renal survival than class IV-G LN (214 months) without statistical significance even though patients with class IV-S showed much higher rate of ESRD. In France, 31 patients with class IV-G LN were compared to 15 patients with class IV-S LN [9]. There was a tendency of worse proteinuria, lower serum hemoglobins, lower complements, and higher sCr in the IV-G LN. Clinical outcome of IV-G LN, however, was similar to the IV-S LN which diagnosed at the first biopsy. This is in accordance with our results where 3 patients with class IV-S and 8 patients with class IV-G showed similar trend of renal response to treatment at one-year follow-up. The distinctive outcome between class IV-S LN and class IV-G LN, however, still remains to be ascertained.

This study has its limitations, mainly stemming from the retrospective design and small sample size. In addition, traditional outcome measures were unavailable due to the fact that only one patient in each group developed ESRD. Thus, the modified renal response criteria were used, which were initially developed to measure the therapeutic efficacy of various pharmaceutical agents [24]. This application may need cautions because treatment modalities were not standardized initially, but there was no statistical difference in the retrospective analysis of treatment between two groups.

In summary, the newly classified ISN-RPS class IV LN from the previous WHO class III LN had higher activity index on the initial biopsy and showed poorer renal response to treatment and inferior outcome in long-term follow-up compared to the remaining class III LN group. Considering the fact that these two groups were originally the WHO class III LN, the revised ISN-RPS classification would be more useful in prognostic guidance and use of optimal treatment agents.

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

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