

# Two Distinct Clinical Courses of Renal Involvement in Rheumatoid Patients with AA Amyloidosis

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**ABSTRACT.** *Objective.* We conducted a prospective study to investigate whether a correlation exists between the clinical course of renal involvement and the pathological findings of renal amyloidosis in patients with rheumatoid arthritis (RA).

*Methods.* Patients with RA of more than 5 years' duration and who did not show renal manifestations were selected and received a duodenal biopsy for the diagnosis of amyloidosis. After the diagnosis of AA amyloidosis, patients received a renal biopsy, and patterns of amyloid deposition were examined. We followed the renal functions (serum levels of blood urea nitrogen and creatinine) of patients diagnosed with AA amyloidosis for 5 years.

*Results.* We diagnosed 53 patients with AA amyloidosis and monitored the renal function of 38 of them for > 5 years. The histological patterns were examined; in the 38 patients there were appreciable variations in the patterns of amyloid deposition. In 27 patients, amyloid deposits were found exclusively in the glomerulus (type 1). In the other 11 patients, however, amyloid deposits were found selectively around blood vessels and were totally absent in the glomerulus (type 2). In type 1 patients with glomerular involvement, renal function deteriorated rapidly regardless of disease state; most patients received hemodialysis. In type 2 patients with purely vascular involvement, however, renal function did not deteriorate significantly.

*Conclusion.* In patients with RA and AA amyloidosis, 2 distinct clinical courses in terms of renal involvement were identified. It is suggested that renal function does not deteriorate when amyloid deposition is totally lacking in the glomerulus. (J Rheumatol 2006;33:1482-7)

## Key Indexing Terms:

AMYLOIDOSIS BIOPSY CREATININE RHEUMATOID ARTHRITIS KIDNEY FAILURE

Amyloidoses form a group of diseases characterized by extracellular deposition of proteins in characteristic amyloid fibrils. These insoluble fibrillar proteins can be localized in one specific site or can be broadly distributed in several vital organs, such as kidneys, liver, spleen, and heart<sup>1</sup>. During fibril formation, elements such as glycosaminoglycans interact with the amyloid protein<sup>2</sup>, promote the structural-shift process, and favor the deposition of fibrils in these organs. Amyloid deposition leads to organ dysfunction, organ failure, and eventually death<sup>3</sup>.

Secondary amyloidosis, which develops secondary to

chronic inflammatory conditions such as rheumatoid arthritis (RA), is now called amyloid-A (AA) amyloidosis because a major factor in the protein deposition process involves the precursor protein AA, a cleaved product of the acute-phase protein serum AA (SAA)<sup>4,5</sup>. AA amyloidosis occurs in a proportion of patients with chronic inflammatory diseases, including RA, ankylosing spondylitis, juvenile RA, and Crohn's disease. Patients with RA represent about 50% of the thousands of patients with AA amyloidosis<sup>6,7</sup>.

Renal involvement is one of the most common features in AA amyloidosis. Renal amyloidosis is diagnosed by renal biopsy, and amyloid deposition is found in different degrees in mesangium, capillary walls, tubules, and blood vessels. The most common and often the earliest site of amyloid deposition in the kidney is the glomeruli, but the blood vessels, the interstitium, and the tubules are also often affected<sup>8,9</sup>.

In patients with RA, AA amyloidosis is reportedly insidious, progressive, and fatal<sup>6</sup>, but little is known about the duration of the subclinical phase because patients can be asymptomatic for a prolonged period<sup>10</sup>. Therefore, clinical diagnosis of AA amyloidosis is often delayed or missed until the amyloid deposits are extensive, and most studies have been carried out retrospectively<sup>11-13</sup>. At the time of diagnosis, many patients with AA amyloidosis have endstage renal disease, and median survival after diagnosis is 4-8 years<sup>14,15</sup>.

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While caring for RA patients with AA amyloidosis, however, we found a group of patients whose renal function remained within normal limits for more than 5 years. We conducted a prospective study examining the correlation between pathohistological findings in the kidney and renal involvement in RA patients with amyloidosis.

## MATERIALS AND METHODS

**Patients and diagnosis of AA amyloidosis.** Patients ( $n = 524$ ) who had had RA for more than 5 years and showed no renal manifestations [serum urea nitrogen (BUN)  $\leq 25$  mg/dl, serum creatinine  $\leq 1.2$  mg/dl, and urea protein  $\leq 200$  mg/day] were selected for study. All patients met the 1987 American College of Rheumatology diagnostic criteria for RA<sup>16</sup>. With all patients' informed consent, duodenum biopsy was performed to diagnose AA amyloidosis. In all patients, amyloid deposition was determined based on positive green birefringence under polarized light in duodenal biopsy sections with Congo red staining<sup>17</sup>. AA protein was immunohistochemically confirmed by the standard avidin-biotin complex method using antibody against AA protein (Dako, Glostrup, Denmark)<sup>12</sup>. After the diagnosis of AA amyloidosis, we performed renal biopsies, and the patterns of amyloid deposition were examined. Patients diagnosed with AA amyloidosis were selected and their clinical courses followed for more than 5 years.

At the time of AA amyloidosis diagnosis, we noted age at onset of RA, disease duration, radiological staging, and drug intake for each patient. Radiological staging was based on the criteria of Steinbrocker, *et al*<sup>18</sup>.

**Measurement of serum samples.** Blood and urine samples were taken every 2 months to examine the level of serum creatinine and BUN, and urinary protein. We also measured serum concentrations of C-reactive protein (CRP) and SAA periodically. CRP (normal range 0–0.3 mg/dl) and SAA (normal range 0–8 mg/dl) were measured with standard ELISA kits in the laboratory.

**Statistical analysis.** We compared data using the Student *t* test. Survival was calculated from the date when amyloid was first observed histologically until the date of death or most recent contact for those still alive. Survival curves were estimated by the Kaplan-Meier technique, and values are given as mean  $\pm$  standard deviation.

## RESULTS

**Histological patterns of renal amyloidosis.** Duodenal biopsy was performed in 524 patients who had had RA  $\geq 5$  years, and 53 cases were diagnosed with AA amyloidosis. From this latter group, we selected cases whose renal function was within normal limits and performed renal biopsies. Fifteen patients dropped out for the following reasons: 7 patients withdrew their informed consent, 4 were lost to followup, and 2 patients moved outside the district. In 2 patients, renal function deteriorated immediately after the diagnosis of amyloidosis, and renal biopsy was not performed.

In specimens stained with Congo red, we examined distribution and amount of amyloid in the kidney (Figure 1). In renal biopsy specimens of 27 patients (71.1%), amyloid deposits were found exclusively in the glomerulus (type 1, glomerular pattern). Among the 27 patients, amyloid deposits were exclusively in the glomerulus ( $n = 7$ ; Figure 1A); but the remainder ( $n = 20$ ) also had amyloid deposits around the blood vessels to varying degrees (Figure 1B, 1C, 1D). In all specimens of the other 11 patients (28.9%) examined, however, amyloid deposits were found selectively around blood vessels and were totally absent in the glomerulus (type 2, iso-

lated vascular pattern; Figure 1E, 1F). Often, arteriolar infiltration stopped abruptly at the glomeruli (Figure 1E). In all patients, the deposition of amyloid was confirmed by a positive green birefringence signal under polarized light in sections from the biopsy specimens with Congo red stain.

**Two distinct clinical courses of renal function in patients with AA amyloidosis.** We divided 38 AA amyloidosis patients into 2 groups, namely type 1 and type 2, according to the renal amyloid deposition patterns, and studied them prospectively. We conducted 5 years of followup studies of clinical data such as BUN and creatinine levels; data for typical cases are illustrated in Figure 2. In type 1 cases, massive proteinuria appeared, and the serum levels of creatinine and BUN increased progressively. Finally, most of the patients began hemodialysis at some time during the 5 years (Figure 2, panels A-D; Table 1). In type 2 cases, however, the serum levels of creatinine and BUN did not deteriorate during the 5-year period (Figure 2, panels E-H; Table 1). When we compared renal function before and after the study, the levels of creatinine and BUN were elevated significantly in type 1 cases, but did not change in type 2. Type 1 patients underwent kidney dialysis within less than 5 years (mean 2.55 yrs), but no type 2 patient began dialysis (Table 1).

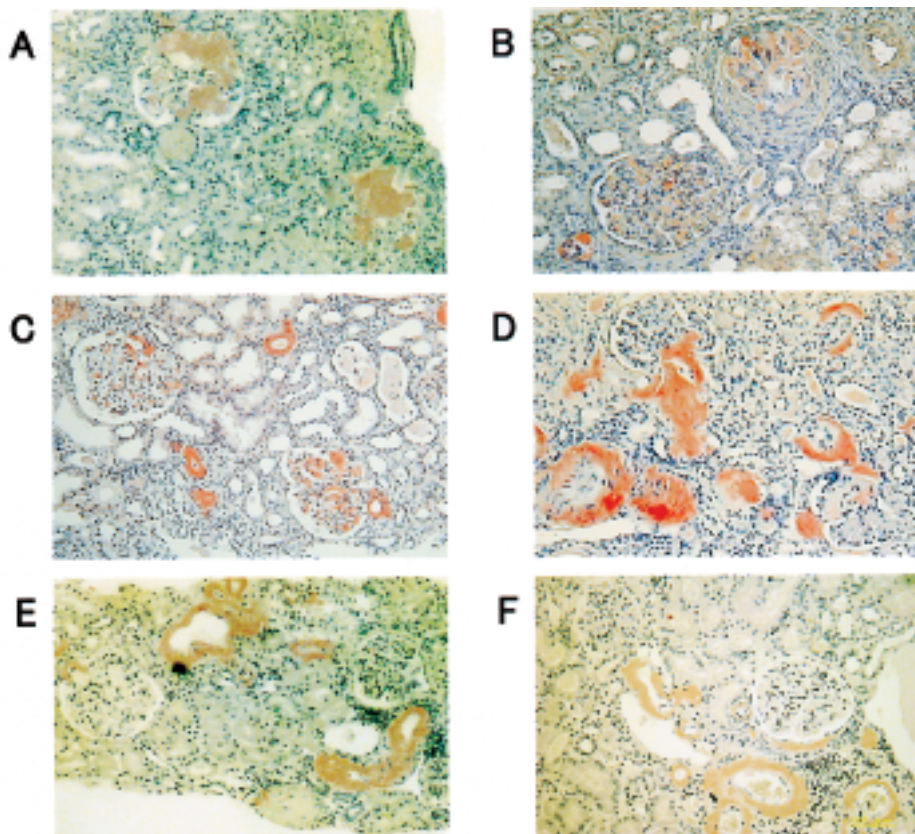
**Comparison of other clinical manifestations.** It is possible that other clinical manifestations, such as the duration of RA, may have contributed to the histological differences; thus, we compared other clinical manifestations between the 2 types of patients (Table 2). Mean age at onset of RA was 39.0 years in type 1 cases and 46.3 years in type 2 ( $p = 0.193$ ). The mean age at diagnosis of amyloidosis in type 1 cases (56.2 yrs) was significantly lower than in type 2 (64.3 yrs;  $p = 0.029$ ). The mean duration of RA in type 1 cases was 17.3 years, and in type 2 18.0 years, suggesting that the difference between the 2 types was not merely the result of disease duration.

We analyzed 32 female and 6 male patients (Table 2). In women, type 1 (75%) disease was more common than type 2 (25%). In men, the distribution of the 2 categories was even (50% vs 50%).

We compared Steinbrocker radiological stage in both types of patients. Most patients from both type 1 and type 2 groups were stage IV (Table 2), suggesting that most RA patients with AA amyloidosis had already progressed radiologically.

Inflammatory processes influence the progression of AA amyloidosis<sup>1</sup>. We also examined levels of the inflammatory indicators CRP and SAA; measures of CRP and SAA seemed to show no significant differences between type 1 and type 2 cases at the diagnosis and at the end of the study (Table 1).

Drug administration was assessed to clarify any differences resulting from medication. At diagnosis, about 40% of patients were being treated with methotrexate (MTX) and 20% with intramuscular gold (Table 2). The percentages of patients being given MTX or intramuscular gold did not differ between the 2 types, and most patients from both groups had received low-dose prednisolone. Other disease modifying



**Figure 1.** Pathohistological patterns of amyloid depositions in the kidney. Representative biopsy sections with Congo red staining are shown. A. Amyloid deposits were found exclusively in the glomerulus. B, C, D. Amyloid deposits found in the glomerulus and around the blood vessels to varying degrees. E, F. Amyloid deposits were found selectively around blood vessels.

antirheumatic drugs (DMARD) such as sulfasalazine or D-penicillamine were used appropriately in consideration of the patient's disease activity. However, each DMARD was used in fewer than 10% of patients.

After the diagnosis of amyloidosis, we carried out conventional therapy such as DMSO and colchicines in most patients. However, we did not use aggressive therapy such as chlorambucil against type 1 disease, but merely increased the dosage of prednisolone (up to 20 mg/day).

*Survival analysis in 2 types of patients with amyloidosis.* Subsequently, we performed a survival analysis of the 2 types of amyloidosis patients with RA. Five-year survival rates from the diagnosis of amyloidosis were 41.2% in type 1 and 90.9% in type 2 disease (Table 1); thus, there was a poorer prognosis for type 1 patients (Figure 3).

## DISCUSSION

We conducted a prospective study instead of a retrospective study to monitor the clinical course of AA amyloidosis in patients with RA. Previously, most investigations of the clinical course of amyloidosis with RA patients have been retrospective<sup>11,12</sup>. Historically, the prognosis of patients with AA amyloidosis is reportedly poor, showing a 50% survival rang-

ing between 2 and 4 years<sup>9,19</sup>. In our study, the 50% survival of patients with type 1 disease was less than 5 years. However, we observed a unique pattern of renal amyloidosis; in this type 2 pattern, the 50% survival is greater than 10 years. This disparity between our data and results from the retrospective studies may partly result from biased selection in other studies: patients with renal manifestations such as proteinuria tended to be investigated by renal biopsy rather than those without or with minor renal manifestations<sup>12,20</sup>. At diagnosis, most patients in the retrospective studies exhibited renal involvement. For this reason, we selected patients who did not exhibit renal involvement at diagnosis. In our study, the diagnosis of amyloidosis was performed by duodenal biopsy instead of renal biopsy. We believe that the patient who has amyloid deposits in the duodenum will also have them in the kidney, as reported<sup>21</sup>. Moreover, in our study, all patients who had amyloid deposits in the duodenum also had them in the kidney.

We clarified that at least 2 clinical courses of renal function exist in patients with RA with amyloidosis. In type 1 disease, renal function deteriorates rapidly, and patients undergo dialysis in less than 5 years; in type 2 disease, renal function does not worsen significantly in 5 years. The clinical pattern of type 1 is similar to that of most patients reported previously<sup>22</sup>. The



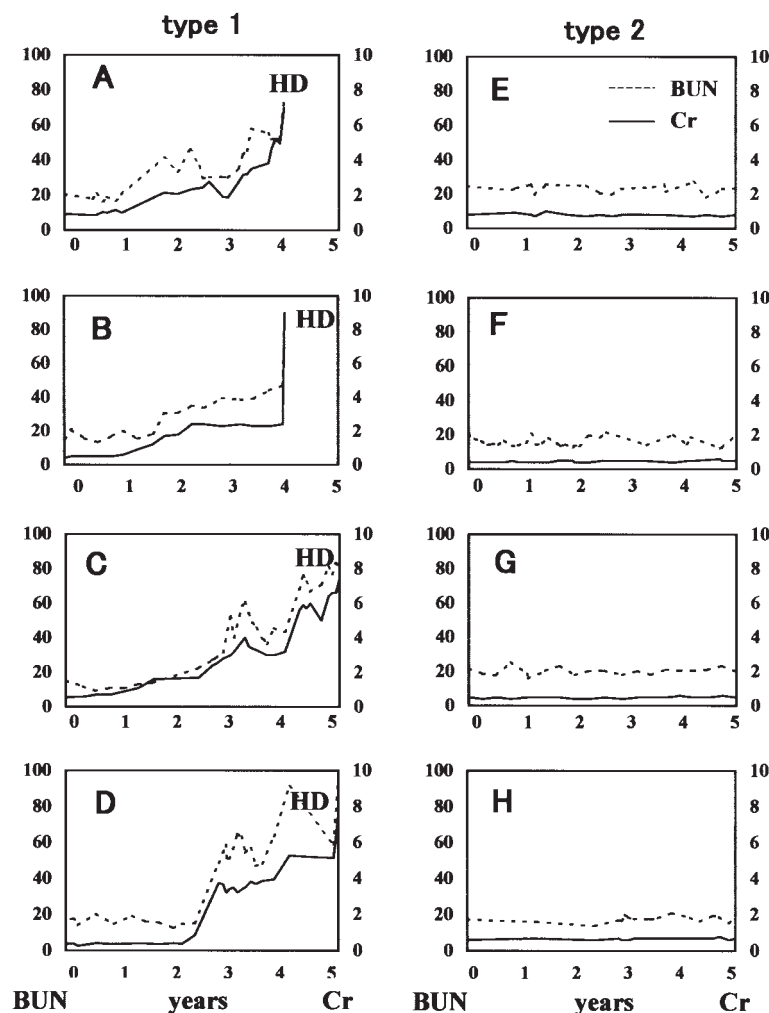


Figure 2. Five years of followup study of levels of serum creatinine (mg/dl) and BUN (mg/dl) in patients with type 1 and type 2 disease; renal function was within normal limits in the 38 cases selected. Representative data for type 1 (panels A-D) and type 2 (E-H) disease are shown. HD: hemodialysis, Cr: creatinine.

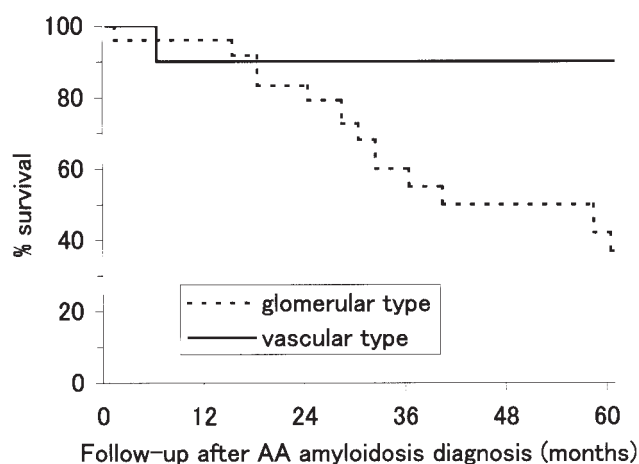


Figure 3. Kaplan-Meier survival curves of patients with type 1 and type 2 renal amyloidosis.

clinical pattern of type 2, however, is quite unusual in patients with AA amyloidosis.

In type 2, amyloid deposits were found around blood vessels and were totally absent in the glomerulus. Indeed, the clinical manifestation of the vascular type is controversial<sup>12,20,23</sup>, but prognosis is reportedly better than that of the glomerular type in leprosy and tuberculosis<sup>12,23</sup>; however, few followup studies of the vascular type exist. Falck, *et al* described 9 RA patients with a predominantly vascular type disease in which the presenting sign was renal failure<sup>20</sup>.

The difference in pathological findings between type 1 and 2 reflects the clinical manifestations. Primarily, glomerular deposition is a critical finding for predicting the clinical course. Renal amyloid deposition is reportedly found to different degrees in glomeruli, blood vessels, tubules, and interstitium<sup>11,12,14</sup>. In our study, however, amyloid deposition was found predominantly in the glomerulus and blood vessels. Our

Table 1. Renal and inflammatory manifestation of RA patients with AA amyloidosis.

	Type 1, n = 27	Type 2, n = 11	p*
Creatinine, mg/dl			
At study entry	0.73 ± 0.57	0.62 ± 0.19	0.521
After 5 yrs**	6.52 ± 1.91	0.71 ± 0.23	< 0.0001
BUN, mg/dl			
At study entry	17.8 ± 7.1	20.7 ± 4.8	0.234
After 5 yrs**	78.6 ± 20.3	20.8 ± 8.0	< 0.0001
Proteinuria, mg/day			
At study entry	71 ± 102	25 ± 60	0.133
After 5 yrs**	2178 ± 1115	48 ± 106	< 0.0001
CRP, mg/dl			
At study entry	2.04 ± 1.66	2.34 ± 1.58	0.617
After 5 yrs**	1.10 ± 1.14	1.42 ± 1.58	0.541
SAA, mg/dl			
At study entry	85.5 ± 83.8	125.4 ± 89.2	0.220
After 5 yrs**	55 ± 66	83 ± 119	0.383
No. of patients on dialysis within 5 yrs	23	0	
Years from diagnosis of amyloidosis to hemodialysis	2.55	0	

\* Type 1 patients versus type 2 patients. \*\* Includes data for last examination of patients who died or underwent hemodialysis.

Table 2. Characteristics of RA patients with AA amyloidosis.

	Total, n = 38	Type 1, n = 27	Type 2, n = 11
No. men/women	6/32	3/24	3/8
Age at RA onset, mean ± SD (range) yrs*	41.1 ± 16.0 (19–71)	39.0 ± 16.5 (19–69)	46.3 ± 14.5 (20–71)
Age at diagnosis of amyloidosis, mean ± SD (range) yrs**	58.4 ± 11.9 (25–77)	56.2 ± 12.6 (25–77)	64.3 ± 8.3 (52–76)
Duration of RA at diagnosis of amyloidosis, mean ± SD (range) yrs***	17.3 ± 10.6 (2–35)	17.3 ± 11.5 (2–35)	18.0 ± 8.7 (5–33)
Radiological grade			
I	0	0	0
II	1	1	0
III	1	0	1
IV	36	26	10
Medication at diagnosis of amyloidosis, %			
Prednisolone (2.5–7.5 mg/day)	94.7	96.3	90.9
DMARD			
MTX (6–10 mg/m <sup>2</sup> /wk)	39.5	37.0	45.5
IM gold (25 mg/4/wks)	21.1	22.2	18.2
Other DMARD†			

\* p = 0.193; \*\* p = 0.029; \*\*\* p = 0.844, type 1 patients versus type 2 patients. † Including oral gold (3 mg twice a day), D-penicillamine (250–500 mg/day), sulfasalazine (500 mg twice a day), azathioprine (50–100 mg/day), cyclosporine (2–4 mg/kg/day), and minocycline (100–200 mg/day) also used in this study. However, each DMARD was used in less than 10% of patients. MTX: methotrexate, DMARD: disease modifying antirheumatic drug, IM: intramuscular.

results reflect the findings of Bohle, *et al* who observed that longterm prognosis of renal amyloidosis is related to the severity of the glomerular amyloidosis<sup>14</sup>. They also found that the longterm prognosis of renal amyloidosis is worse if acute renal failure or interstitial fibrosis is present at the time of the biopsy.

We considered why several different patterns of amyloid depositions occurred. There is no clear explanation for the mechanism underlying differences in amyloid deposition<sup>9</sup>. Chronic inflammation that gives rise to an acute-phase protein

response is a prerequisite to the development of AA amyloidosis<sup>1</sup>. In our study, the level of CRP or SAA seemed to show no significant differences between type 1 and type 2. At present, we believe the difference is not explained merely by these inflammatory variables. It is tempting to consider the glomerular pattern as merely a more advanced stage of renal amyloidosis compared with the vascular pattern<sup>23</sup>. But this suggestion can be refuted by the fact that the duration of RA did not differ between the 2 disease types.

In all cases examined, the amyloid deposits were shown to

be of the AA type, which excludes the possibility that the vascular deposition of amyloid resulted from the presence of other types of systemic amyloidosis. Differences in serum amyloid-degrading activity might explain the differences in amyloid deposition pattern<sup>5</sup>. The concept that genetically and chemically different amyloid proteins manifest differing patterns of amyloid deposition is most plausible. Recently, polymorphisms of the SAA protein were linked to differences in amyloidosis<sup>24</sup>, but we found no difference in our preliminary experiments. Further studies will be required to investigate this possibility.

Successful treatment of AA amyloidosis reportedly depends on successful treatment of the underlying disease<sup>25,26</sup>. In patients exhibiting the glomerular pattern of amyloidosis, however, we found that renal function deteriorated regardless of treatments. We did not carry out aggressive therapy such as chlorambucil in patients with type 1 disease, but merely increased the dosage of prednisolone, because the usage of chlorambucil is not permitted in Japan. Moreover, during the study, use of the newer biological drugs also was not permitted in Japan. More recently, successful treatment of patients with RA and amyloidosis using anticytokine therapy has also been reported<sup>27,28</sup>, leaving the possibility that anticytokine therapy might improve the prognosis of patients with type 1 AA amyloidosis.

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