Elevated Levels of High-Sensitivity C-Reactive Protein and Serum Amyloid-A Late After Kawasaki Disease
Association Between Inflammation and Late Coronary Sequelae in Kawasaki Disease

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Background—Coronary sequelae that persist after Kawasaki disease (KD) have been associated with obstructive changes of the lesions and coronary vascular events in adolescents and young adults. However, little is known about the association between sequelae late after KD and inflammatory markers, which are potential mediators and markers for atherogenesis.

Methods and Results—Cross-sectional study was performed to test the hypothesis that coronary sequelae are associated with elevated levels of inflammatory markers in patients late after KD (mean time interval after the onset, 10 years, 10 months). Levels of high-sensitivity C-reactive protein (CRP), serum amyloid-A (SAA), interleukin-6, and soluble intercellular adhesion molecule-1 were measured in the 4 groups (n=80): the referent group (n=15) and KD subgroups with normal coronary arteries from the onset (n=27); with regressed aneurysms (n=18); and with coronary artery lesions, such as persistent aneurysms, stenosis, and occlusion (n=20). CRP levels were significantly elevated in a KD subgroup with coronary artery lesions compared with the referent or other KD subgroups, as analyzed by ANOVA and ANCOVA after adjustment for a confounding factor body mass index. Levels of CRP, SAA, and interleukin-6 were positively correlated. Stepwise regression and logistic regression analyses support the association between the persistence of coronary artery lesions and the levels of CRP and SAA.

Conclusions—Results demonstrate that the persistence of coronary lesions late after KD was independently associated with levels of CRP and SAA, suggesting that inflammation may be a novel functional aspect of coronary artery diseases late after KD.

Key Words: atherosclerosis ■ coronary disease ■ risk factors ■ pediatrics ■ prevention

Kawasaki disease (KD) is an acute febrile disorder with coronary and other systemic vasculitis that occurs predominantly in infancy and early childhood. This disease is of great concern to pediatricians, because approximately 15% to 25% of the patients develop coronary aneurysms, leading to angina pectoris, myocardial infarction, or sudden death. To date, >100 000 children have been affected by KD in Japan for >35 years after the first report, whereas in the United States, KD is the leading cause of acquired heart disease in childhood. Later in adulthood, angiographic and postmortem studies demonstrated that coronary sequelae persisting long after acute KD vasculitis predispose to arteriosclerotic changes, which are associated with late coronary events or sudden death. However, the mechanisms underlying the late coronary vascular diseases are poorly understood.

Functional aspects of vascular diseases late after KD have been reported only recently. Impairment in endothelial function was demonstrated in patients late after KD by quantitative coronary angiography using acetylcholine infusion or by ultrasound study of peripheral vessel responses to reactive hyperemia in recent reports, including ours. With the recent recognition that atherosclerosis is an inflammatory disease, as demonstrated in animal models and human, several inflammatory markers, especially high-sensitivity C-reactive protein (CRP) and serum amyloid-A (SAA), have recently been regarded as reliable clinical markers for the
prediction of coronary events, independent of other known risk factors for coronary diseases. However, the association between coronary sequelae late after KD and levels of inflammatory markers for atherosclerosis is still unknown.

We therefore hypothesized that the persistence of coronary arterial lesions (CALs) late after KD is associated with elevated levels of inflammatory markers. We investigated the serum levels of CRP and SAA, as well as other inflammatory markers, in referents and patients with or without CALs late after KD. The association between the presence of CALs in KD patients and levels of inflammatory markers was analyzed by univariate and multivariate analyses.

Methods

To perform a cross-sectional study, levels of inflammatory markers were compared among groups with a history of KD and an age-matched referent group. KD patients were categorized into 3 groups on the basis of the long-term sequelae, as evaluated by echocardiography and/or coronary angiography: KD patients with no coronary aneurysms or ectasia from the disease onset; those with regressed aneurysms; and those with persistent CALs, including aneurysms, stenosis, and occlusion. A coronary artery during the acute phase was defined as aneurysmal if the internal luminal diameter was ≥3 mm in children younger than 5 years of age or ≥4 mm in children 5 years old or older, or if the diameter of the segment was ≥1.5 times that of the adjacent segment. The CALs in the long term were described according to standardized criteria. The study protocol was approved by the ethics committee of Mie University School of Medicine. The procedures followed were in accordance with institutional guidelines. Written informed consent was taken from each patient and/or his or her parents.

Study Subjects

Consecutive KD subjects meeting the following criteria were recruited from the outpatient clinics in Mie University Hospital, Mutsuoka City Hospital, Tenri Hospital, and Hyogo Children’s Hospital between August 2002 and August 2003: (1) a diagnosis of KD; (2) echocardiographic evaluation of CALs in the acute phase of the illness and regular follow-up by use of echocardiography and/or coronary angiography, if indicated, until the time of the examination; and (3) the interval between the disease onset and the time of the investigation ≥5 years. Referent patients without a history of KD (n=15) included 10 age-matched consecutive patients with trivial congenital heart diseases and 5 age-matched consecutive patients with abnormal ECG findings in an outpatient clinic in Mie University hospital.

All the patients underwent detailed clinical examination for the assessment of general and cardiac conditions. Patient records were collected to evaluate the cardiac status. Exclusion criteria included infectious diseases and injury within 1 month before the study, chronic inflammatory disease, malignancy, ejection fraction <0.6, and clinical evidence of heart failure.

Laboratory Measurements

Venous blood samples were collected at the time of the clinical examination and stored at −80°C before analysis. CRP levels were measured in the serum by use of a commercially available high-sensitivity method (Dade Behring). SAA levels were measured with latex-enhanced immunoassay (Eiken Kagaku) that could detect concentrations as low as 2.6 μg/mL. Serum levels of interleukin-6 (IL-6) (Fuji Lebio) and soluble intercellular adhesion molecule-1 (sICAM-1) (R & D Systems) were measured by a high-sensitivity ELISA that allowed detection of levels as low as 0.3 pg/mL and 11 ng/mL, respectively. All measurements were performed in a single batch at the end of the study, and the laboratory staffs were blinded to the clinical data.

Statistical Analysis

All statistical analysis was performed with SPSS 11.0J for Windows (SPSS Inc.). For the analysis of clinical characteristics, the significance of any difference in means among 3 or 4 groups was tested with a 1-way ANOVA, followed by a Scheffé’s F test; differences in proportions were tested with the χ2 analysis. Because values of CRP, IL-6, and sICAM-1 have a skewed distribution, median concentrations were computed for these parameters, and the significance of any differences among the 4 groups was assessed by use of Kruskal Wallis test, followed by Mann-Whitney U test adjusted with a Bonferroni correction for multiple comparisons: adjusted probability values were reported after multiplying each probability value by 6. Logarithmically transformed values (natural logarithm) were also used, because the distribution of the residuals from the fitted models becomes normally distributed after logarithmic transformation. The values of logarithmically transformed values of CRP, IL-6, and sICAM-1 were used for the subsequent statistical analysis. Levels of these values among the 4 groups were evaluated by ANOVA, followed by Scheffé’s F test. After adjustment for body mass index, these values were compared by ANCOVA, in which a Bonferroni correction was applied for multiple comparison. Because levels of SAA were below the lowest detectable level in many patients, the proportions of patients above and below the lowest detectable level in patient groups were compared by χ2 analysis. The correlation was analyzed with Pearson and/or Spearman correlation coefficients in KD patients. Partial correlations (adjusting for covariables: age, smoking, body mass index, family history of ischemic heart disease, systolic blood pressure, and total cholesterol/HDL cholesterol) for CRP, IL-6, and sICAM-1 were also calculated. To assess the relative strength of independent association of these values with clinical factors in KD patients, we used a stepwise multiple regression analysis (CRP, IL-6, and sICAM-1) and a logistic regression analysis (SAA). In stepwise regression analysis, we used log CRP, log IL-6, and log sICAM-1 values as dependent variables and evaluated the order of inclusion in the model of the following variables: age, smoking, body mass index, the presence of family history, systolic blood pressure, the total cholesterol/HDL cholesterol ratio, and coronary lesions. In a logistic regression analysis, we used similar variables to adjust for their potential effects on the SAA subgroups above or below 2.6 μg/mL. Data are reported as mean±SEM or median±interquartile range, and a value of P<0.05 was accepted as statistically significant.

Results

Patient Sample

Seventy KD patients and 15 referent patients were screened for the study. Five of these KD patients were excluded from the recruitment because of a history of acute infection. The remaining 65 patients late after KD and 15 age-matched referent subjects were enrolled in this study. The KD patients included 3 subgroups on the basis of the long-term sequelae: KD patients (n=27) with no coronary aneurysms or ectasia from the disease onset; those (n=18) with regressed aneurysms; and those (n=20) with persistent CALs, including aneurysms (n=10), stenosis (n=6), and occlusion (n=4). The coronary angiography was performed in 5 of 27 KD patients with normal coronary arteries, in 16 of 18 KD patients with regressed aneurysms, and in all 20 patients with persistent CALs. Nineteen of 20 patients with persistent CALs took regular antiplatelet agents, of which 17 patients took antiplatelet doses of aspirin, 8 took dipyridamole, and 2 took ticlopidine. One patient with persistent CALs had acute myocardial infarction more than 10 years earlier. Forty-eight of 62 KD patients for whom the information about the treatment during the acute illness is available were treated with various doses of intravenous γ-globulin: 18 of 25
patients with normal coronary arteries from the acute illness, 17 of 18 patients with regressed aneurysms, and 13 of 19 patients with persistent CALs received γ-globulin treatment during the acute illness. The detailed clinical characteristics of patients were described in the Table. All the 4 groups have similar characteristics with respect to height, body weight, body mass index, sex, the presence of family history of ischemic heart disease (one positive subject in a KD subgroup with normal coronary arteries; one in a KD subgroup with CALs), smoking (2 subjects only in a KD groups with normal coronary arteries), diabetes (none in any subgroups), age at the investigation, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and the total cholesterol/HDL cholesterol ratio. Three KD subgroups have similar values with respect to age at the onset of KD and the time interval between the onset and the time of investigation.

Levels of CRP, SAA, IL-6, and sICAM-1
Levels of CRP were higher in KD patients with persistent CALs (median and interquartile ranges: 0.29, 0.19 to 0.38 mg/L) than in referents (0.09, 0.05 to 0.19 mg/L) (adjusted probability value, $P=0.012$), in KD patients with normal coronary arteries (0.13, 0.07 to 0.19 mg/L) (adjusted probability value=0.006) and in those with regressed aneurysms (0.11, 0.03 to 0.23 mg/L) (adjusted probability value, $P=0.072$), as analyzed by Kruskal-Wallis test, followed by Mann-Whitney $U$ test adjusted with a Bonferroni correction for multiple comparisons (Figure 1A). Because 56 of 80 patients have levels of SAA below the lowest detectable level, the differences of the proportions of patients with levels ≥2.6 and <2.6 μg/mL among the 4 groups were analyzed by $\chi^2$ analysis. The proportions of SAA ≥2.6 μg/mL were higher in KD patients with persistent CALs ($≥2.6/<2.6 \mu g/mL$, 14/6) than those in referents (3/12) and in KD patients with normal coronary arteries (3/24) and with regressed aneurysms (4/14) ($P=0.001$). Levels of IL-6 were similar among the 4 groups, although IL-6 levels tend to be higher in KD patients with persistent CALs (0.90, 0.60 to 1.30 pg/mL) than in referents (0.70, 0.50 to 0.95 pg/mL) and in KD patients with normal coronary arteries (0.60, 0.50 to 1.00 pg/mL) and with regressed aneurysms (0.70, 0.50 to 0.90 pg/mL) ($P=NS$) (Figure 1A). There were no differences in sICAM-1 levels among the 4 groups.

Logarithmically transformed levels of CRP were significantly higher in KD patients with persistent CALs than in referents and in KD patients with normal coronary arteries and with regressed aneurysms, as analyzed by ANOVA ($P<0.05$) and by ANCOVA ($P<0.05$) after adjustment for body mass index (Figure 1, B and C). Logarithmically transformed levels of IL-6 were similar among the 4 groups, although IL-6 levels tend to be higher in KD patients with persistent CALs than in referents and in KD patients with normal coronary arteries and with regressed aneurysms, as analyzed by ANOVA and ANCOVA ($P=NS$) (Figure 1, B and C). There were no differences in logarithmically transformed levels of sICAM-1 among the 4 groups.

Correlation Between Levels of CRP, SAA, IL-6, and sICAM-1
In KD patients, logarithmically transformed levels of CRP were positively correlated with IL-6 ($r=0.56$, $P<0.001$) but not with sICAM-1, as analyzed by Pearson’s correlation coefficients (Figure 2). After adjustment for confounding factors, levels of CRP were positively correlated with IL-6 ($r=0.56$, $P<0.001$) but not with sICAM-1, as analyzed by partial correlation coefficients.

### Table: Clinical Characteristics of Subgroups After Kawasaki Disease and Referent Subjects

<table>
<thead>
<tr>
<th>Referent (n=15)</th>
<th>Normal (n=27)</th>
<th>Regression (n=18)</th>
<th>CAL (n=20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean</td>
<td>159 ± 11</td>
<td>161 ± 10</td>
<td>147 ± 8</td>
<td>165 ± 13</td>
</tr>
<tr>
<td>Age at KD, mean</td>
<td>...</td>
<td>26 ± 5</td>
<td>27 ± 6</td>
<td>35 ± 8</td>
</tr>
<tr>
<td>Interval, mean</td>
<td>...</td>
<td>135 ± 11</td>
<td>121 ± 12</td>
<td>130 ± 12</td>
</tr>
<tr>
<td>Height, cm</td>
<td>152 ± 4</td>
<td>151 ± 3</td>
<td>148 ± 4</td>
<td>151 ± 4</td>
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<tr>
<td>BW, kg</td>
<td>45 ± 3</td>
<td>44 ± 3</td>
<td>41 ± 3</td>
<td>45 ± 3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>19.0 ± 0.6</td>
<td>18.9 ± 0.6</td>
<td>18.1 ± 0.7</td>
<td>19.3 ± 0.6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>109 ± 3</td>
<td>111 ± 1</td>
<td>107 ± 2</td>
<td>108 ± 2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>64 ± 2</td>
<td>59 ± 2</td>
<td>62 ± 2</td>
<td>64 ± 2</td>
</tr>
<tr>
<td>Tchol, mg/dL</td>
<td>163 ± 9</td>
<td>162 ± 6</td>
<td>177 ± 9</td>
<td>153 ± 8</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>56 ± 3</td>
<td>64 ± 3</td>
<td>67 ± 3</td>
<td>65 ± 5</td>
</tr>
<tr>
<td>Tchol/HDL ratio</td>
<td>2.8 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>2.6 ± 0.2</td>
</tr>
<tr>
<td>Medication</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>CAG</td>
<td>0 (0)</td>
<td>5 (19)</td>
<td>16 (89)</td>
<td>20 (100)</td>
</tr>
</tbody>
</table>

$P$ indicates probability value, mg/L) than in referents (0.09, 0.05 to 0.19 mg/L) (adjusted probability value, $P=0.012$), in KD patients with normal coronary arteries (0.13, 0.07 to 0.19 mg/L) (adjusted probability value=0.006) and in those with regressed aneurysms (0.11, 0.03 to 0.23 mg/L) (adjusted probability value, $P=0.072$), as analyzed by Kruskal-Wallis test, followed by Mann-Whitney $U$ test adjusted with a Bonferroni correction for multiple comparisons (Figure 1A). Because 56 of 80 patients have levels of SAA below the lowest detectable level, the differences of the proportions of patients with levels ≥2.6 and <2.6 μg/mL among the 4 groups were analyzed by $\chi^2$ analysis. The proportions of SAA ≥2.6 μg/mL were higher in KD patients with persistent CALs ($≥2.6/<2.6 \mu g/mL$, 14/6) than those in referents (3/12) and in KD patients with normal coronary arteries (3/24) and with regressed aneurysms (4/14) ($P=0.001$). Levels of IL-6 were similar among the 4 groups, although IL-6 levels tend to be higher in KD patients with persistent CALs (0.90, 0.60 to 1.30 pg/mL) than in referents (0.70, 0.50 to 0.95 pg/mL) and in KD patients with normal coronary arteries (0.60, 0.50 to 1.00 pg/mL) and with regressed aneurysms (0.70, 0.50 to 0.90 pg/mL) ($P=NS$) (Figure 1A). There were no differences in sICAM-1 levels among the 4 groups.
Factors Independently Associated With Levels of CRP, SAA, IL-6, and sICAM-1

To examine the independent predictors of logarithmically transformed levels of CRP, IL-6, and sICAM-1, we performed a stepwise regression analysis in KD patients. Among the clinical variables, the only predictor of levels of CRP was the presence of CALs (B = 0.93 ± 0.27, R = 0.40, P = 0.001). The predictor of levels of IL-6 was body mass index (B = 0.06 ± 0.02, R = 0.32, P = 0.01), not the presence of CALs. No factors were independent predictors of sICAM-1. To examine the independent predictors of SAA levels ≥ the lowest detectable level in KD patients, we performed a logistic regression analysis. The presence of CALs was an independent predictor of positive SAA levels (OR = 7.12; 95% CI, 1.82 to 27.77; P = 0.005).

Discussion

The present study provides a novel observation that the levels of the inflammatory markers CRP and SAA are elevated in KD patients with CALs, compared with the referents, or with other KD subgroups with normal coronary arteries or with regressed aneurysms, in the long-term follow-up period. Levels of CRP, SAA, and IL-6 were positively correlated. The persistence of CALs was independently associated with the levels of CRP and SAA. These findings suggest that inflammation may be a novel functional aspect of coronary artery diseases associated with KD in the long term.

The CRP and SAA levels in KD patients can be influenced by other factors related to CALs. Several recent reports in an apparently healthy population demonstrated that CRP levels are significantly associated with several cardiovascular risk factors: age, smoking, body mass index, and lipid-based risk factors. However, the confounding effects of these factors (ie, especially body mass index) on the association with KD are unlikely, because our study groups have similar characteristics with respect to coronary risk factors and because analyses by ANCOVA after adjustment for body mass index and multivariate analysis further support the association. It seems to be unlikely that our results reflect ongoing subclinical ischemia or acute infection, which might have led to inadvertent elevations of both CRP and SAA. In this regard, the levels of CRP and SAA described in these data are substantially below those typically associated with the acute-phase response. Furthermore, elevations of CRP and SAA associated with acute myocardial infarction return to baseline within 8 to 10 days, whereas those associated with acute infection may return to the normal range within 2 to 3 weeks. Because blood samples in our study were obtained at least 4 weeks after the acute infection, inadvertent bias on this basis seems unlikely.

Levels of CRP may be affected by the difference in medication among study groups, because most of our KD patients with persistent CALs, but not those with normal coronary arteries or regressed aneurysms, took aspirin, dipyridamole, or ticlopidine. In fact, a recent study demonstrated that aspirin decreases CRP levels in adult patients with chronic stable angina, although this is still controversial. Therefore, it is possible that elevated CRP levels in the KD subgroup with CALs might rather have been underestimated, if anything, not overvalued, by such medication. The strong association between CALs after KD and levels of CRP and SAA is further supported by the present finding that the levels
of CRP and SAA were positively correlated with those of IL-6. These findings were consistent with the mechanisms by which both CRP and SAA are produced in the liver in response to circulating cytokines, including IL-6. The reason why levels of IL-6 were not associated with the presence of CALs, whereas they were correlated with those of CRP and SAA, is unknown. IL-6 might be a less sensitive marker for some mechanisms related to CALs in KD patients, as is the case with acute coronary events in adult patients, in which CRP and SAA have higher predictive power of coronary events than IL-6 and sICAM-1.

Inflammatory responses observed in patients late after KD are consistent with previously documented endothelial dysfunction in such patients. Impaired endothelial function has been demonstrated in KD patients with CALs in previous studies. Because endothelium-derived nitric oxide (NO) inhibits the expression of adhesion molecules, decreased NO release may upregulate the expression of these molecules. In addition, because NO has antioxidant properties, the decreased NO production may unmask local inflammatory responses. Conversely, CRP directly reduces NO production by endothelial cells and increases endothelial expression of adhesion molecules. The exposure of endothelial cells to proinflammatory cytokines impairs endothelium-dependent vasorelaxation. In fact, in patients with ischemic heart diseases in adults, elevated CRP levels are associated with impaired endothelium-dependent relaxation. In KD patients, coronary endothelial function was impaired in patients with CALs but not in those with normal coronary arteries, although this is still controversial. Therefore, elevated CRP levels might be associated with endothelial dysfunction observed in KD patients in the long term.

Evidence indicative of inflammatory responses may offer a clue to the understanding of the mechanisms involved in acute coronary events in adults with a history of KD. Autopsy studies in these patients revealed persistent aneurysms with or without stenosis, which is associated with thrombosis. It is interesting to speculate that exaggerated procoagulant activity induced by exposure of endothelium to proinflammatory cytokines as well as by decreased NO production may lead to such thrombotic events. Alternatively, thrombus attached to coronary aneurysms and other lesions by the local rheological changes produced by an aneurysmal surface may activate inflammatory cascades via thrombin-mediated pathways: endothelial P-selectin and platelet-activating factor expression, and platelet-derived CD 40 ligand release, culminating in inducing inflammatory cytokines, including IL-6. These lines of evidence may suggest that inflammation may be a novel functional aspect of coronary artery diseases late after KD.

Elevated inflammatory markers may be associated with premature development of atherosclerosis in KD. Recent reports showed that inflammatory processes play a pivotal role in atherogenesis, which may account for initiation and progression of atherosclerosis. CRP is referred to as an acute-phase protein with multiple biological effects that may mediate several steps in the initiation and/or progression of atherosclerotic lesions. Recent data indicated that CRP levels add to the predictive value of standard measurements in determining the risk of the first myocardial infarction. In addition, coronary sequelae late after KD have been associated with an active remodeling process accompanied by expression of growth factors. Therefore, the present data are consistent with the hypothesis that the inflammatory process may be involved in the progression of CALs late after KD and coronary events in adolescents and young adults.

Limitations
Several limitations should be considered in interpreting our results. First, CRP levels were not elevated in KD patients with normal coronary arteries or regressed aneurysms in the present study. These findings suggest that inflammatory processes may not work in normal coronary arteries or regressed aneurysms in KD. However, the possibility that localized inflammation persists in coronary arteries in these mild cases cannot be excluded in the present study. Because Kawasaki vasculitis is heterogeneous in the systemic vasculature, most prominently in coronary arteries, low-grade and local inflammation may still remain undetected in these vessels. Second, our study design was cross-sectional. In this regard, the predictive value of CRP with respect to the coronary events in KD was not determined. Therefore, the present study warrants a cohort study. Third, the effects of the differences of the regimen of γ-globulin therapy during the acute illness and antiplatelet agents in the long-term on inflammatory markers were undetermined in the present study because of the limitation of the number of the KD patients with persistent CALs.

Implications
The evidence of inflammatory responses, as well as of endothelial dysfunction, in patients late after KD is consistent with the hypothesis that a history of KD associated with persistent CALs may be a risk factor for atherosclerosis or coronary vascular events in adulthood, even in the absence of hypercholesterolemia. Because of the emerging interest in primary prevention of atherosclerotic cardiovascular diseases beginning in childhood, the history of KD associated with CALs could be considered in this regard. A recent study showed that the potential effect of inflammation on coronary risk is attenuated by statin therapy in patients with relatively low cholesterol levels, suggesting the intriguing possibility that statin therapy may be useful for the prevention of future cardiovascular risks in KD patients via antiinflammatory mechanisms. Likewise, the use of aspirin at higher doses, β-blockers, or ACE inhibitors might be considered for KD patients with respect to antiinflammatory mechanisms. Similarly, avoidance of other risk factors, including smoking, obesity, and sedentary lifestyle, could be recommended for the appropriate KD patients.

References


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