The thymus and activation-regulated chemokine (TARC) level in serum at an early stage of a drug eruption is a prognostic biomarker of severity of systemic inflammation

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Abstract

Background: In severe drug eruptions, precise evaluation of disease severity at an early stage is needed to start appropriate treatment. It is not always easy to diagnose these conditions at their early stage. In addition, there are no reported prognostic biomarkers of disease severity in drug eruptions. The aim of this study was to test whether the thymus and activation-regulated chemokine (TARC) level in serum at an early stage of a drug eruption can serve as a prognostic biomarker of systemic inflammation.

Methods: Study participants included 76 patients who received a diagnosis of a drug eruption, one of the following: drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, maculopapular exanthema, and erythema multiforme. Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) was eliminated in this study because scoring system for evaluating the severity was established. Correlation coefficients between serum TARC levels and indicators of systemic inflammation, including the neutrophil-to-lymphocyte ratio, Glasgow prognostic score, modified systemic inflammatory response syndrome (mSIRS) score, and C-reactive protein in serum were evaluated.

Results: Serum TARC levels positively correlated with the neutrophil-to-lymphocyte ratio, Glasgow prognostic score, mSIRS score, C-reactive protein, albumin, white blood cell count, body temperature, and pulse rate. TARC levels negatively correlated with systolic blood pressure. Among these parameters, the mSIRS score showed strong correlation (correlation coefficient: 0.68).

Conclusions: Serum TARC levels correlate well with indicators of systemic inflammation and of disease severity among patients with a drug eruption except SJS/TEN. Serum TARC may be a prognostic biomarker of severity of inflammation in drug eruptions.

Introduction

Because drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) is life-threatening drug eruptions, precise evaluation of disease severity
at an early stage is needed to start appropriate treatment and to improve the prognosis. However, it is not always easy to diagnose these conditions at early stages.\textsuperscript{1–3}

Several indicators are known as a useful scoring system for systemic inflammation, including the neutrophil-to-lymphocyte ratio (NLR),\textsuperscript{4} Glasgow prognostic score (GPS),\textsuperscript{5,6} and systemic inflammatory response syndrome (SIRS) score.\textsuperscript{7,8} Especially, worsened vital signs, which are included in the SIRS score, can lead to mortality in patients with DRESS.\textsuperscript{9} Although the scoring system for evaluating severity of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) was reported,\textsuperscript{10} there are no reported biomarkers that can predict severity of drug eruptions.

Thymus and activation-regulated chemokine (TARC; i.e., CC chemokine ligand 17) recruits Th2-polarized T lymphocytes into local inflammation sites, thus leading to a Th2-type immune reaction.\textsuperscript{11–13} Recently, TARC has been given a lot of attention as a potential biomarker of drug eruptions.\textsuperscript{14,15} Serum TARC levels are elevated preferentially in patients with DRESS/DIHS,\textsuperscript{14,16} reflecting a Th2-type immune response in these patients.\textsuperscript{10} On the other hand, we recently demonstrated that serum TARC levels increase in association with eosinophilia in patients with a drug eruption, regardless of DRESS/DIHS.\textsuperscript{17}

In the present study, we aimed to test whether serum TARC at an early stage of a drug eruption can serve as a prognostic biomarker of systemic inflammation.

\textbf{Methods}

\textbf{Patients}

Study participants included 76 patients (10–99 years old; mean age 61.1) who received a diagnosis of a drug eruption in Shimane University Hospital from April 2014 to October 2016. Of the 76 patients, 28 were males (10–89 years old; mean age 65.1), and 48 were females (19–99 years old; mean age: 59.1). Diagnoses of DRESS/DIHS were made according to the respective clinical criteria.\textsuperscript{14–17} Final diagnoses were made as follows: DRESS/DIHS was used for evaluating the SIRS (mSIRS) score was used for evaluating the

\begin{itemize}
  \item WBC count, BT, and PR, with the highest score of 3 and lowest score of 0 (Table 2), where the respiratory rate was omitted from the original SIRS scoring system because such data were scarce. The worst levels of respective clinical parameters or clinical scores during a medical examination were used for evaluation of a correlation with serum TARC levels.
\end{itemize}

\textbf{Measurement of serum TARC levels}

Serum TARC levels were quantified by a chemiluminescent enzyme immunoassay using the HISCL\textsuperscript{®} system (Sysmex, Hyogo, Japan) and a TARC Assay Kit (Shionogi, Osaka, Japan).\textsuperscript{19} Serum TARC levels were examined at first visit to Shimane University Hospital. The mean lag of TARC measurement after onset was 7.1 ± 8.3 days.

\textbf{Data analysis}

The data are presented as mean ± standard deviation. Statistical analysis was conducted in the R software (version 3.3.1, Vienna, Austria). The Mann–Whitney U test was used for analysis between two groups. The Kruskal–Wallis test was performed for comparison among three or more groups. The Spearman’s rank correlation test was carried out for analysis of correlations. Statistical significance was assumed when a P value was less than 0.05.

\textbf{Results}

\textbf{The NLR, GPS, and mSIRS score in the groups of patients stratified by diagnosis}

When the NLR was evaluated during the disease course in the respective groups, the values were 18.5 ± 21.0 in the DRESS/DIHS (n = 11), 4.5 ± 2.8 in MPE (n = 18), and 12.0 ± 28.0 in EM (n = 46). The NLR was higher in the DRESS/DIHS than in MPE (P = 0.001) (Fig. 1A). GPS was 1.70 ± 0.48 in the DRESS/DIHS (n = 10), 0.44 ± 0.51 in MPE (n = 16), and 1.02 ± 0.85 in EM (n = 44). GPS in the patients with the DRESS/DIHS was higher than GPS in the patients with MPE and EM (P < 0.001 and P = 0.018, respectively) (Fig. 1B). The mSIRS score was 2.20 ± 0.63 in DRESS/DIHS (n = 10), 0.58 ± 0.79 in MPE (n = 12), and 1.09 ± 1.13 in EM (n = 34). The mSIRS scores in the patients with DRESS/DIHS were higher than these scores in the patients with MPE and EM, (P = 0.002 and P = 0.003, respectively) (Fig. 1C).

\textbf{Laboratory and physical parameters in the groups of patients stratified by diagnosis}

The data on laboratory and physical parameters are presented in Table 3, including the WBC count, neutrophil count, lymphocyte count, CRP, Alb, BT, PR, sBP, and dBP in the groups of patients stratified by diagnosis. When these values were compared among the groups, the CRP level was higher in the patients with DRESS/DIHS than in patients with MPE and EM (P = 0.001 and P = 0.042,
respectively); BT was higher in the patients with DRESS/DIHS than in patients with MPE and EM ($P = 0.004$ and $P = 0.005$, respectively); sBP was lower in the patients with DRESS/DIHS than in patients with MPE, and EM ($P < 0.001$, and $P = 0.005$, respectively); dBP was lower in the patients with DRESS/DIHS than in patients with MPE ($P = 0.041$).

**Correlations between serum TARC levels and indicators of systemic inflammation**

When serum TARC levels were evaluated at the first examination, the data in the groups of patients stratified by diagnosis were as follows: $32.156 \pm 22.566$ pg/mL in DRESS/DIHS, $2033 \pm 4548$ pg/mL in MPE, and $3461 \pm 5681$ pg/mL in EM. The serum TARC level was higher in DRESS/DIHS than in MPE, and EM (respective $P$ values were all less than $0.001$) (Supplementary Fig. 1).

Positive correlations were found between serum TARC levels and WBC count, neutrophil count, CRP, BT, and PR, whereas negative correlations were detected between serum TARC levels and Alb, and sBP (Fig. 2). A significant correlation was observed between serum TARC levels and NLR, GPS, and mSIRS score, all of which were positive correlations (Fig 3). Among these parameters, the mSIRS score showed strong correlation (correlation coefficient: $0.68$). In addition, most of these correlations remained significant even if we included only patients with MPE, and EM, omitting patients with DRESS/DIHS (Supplementary Fig. 2, 3). And most of these tendencies were observed in the respective patient groups (Supplementary Fig. 4, 5).

**Receiver-operator characteristic curve (ROC) analysis**

To assess the utility of serum TARC measurements for prognosis of systemic inflammation, a receiver-operator characteristic curve (ROC) analysis was conducted. Serum TARC measurements were found to have sensitivity $72\%$ and specificity $70\%$ for the GPS of $2$ with a cutoff value of $2000$ pg/mL ($n = 69$). Serum TARC levels had sensitivity $83\%$ and specificity $64\%$ for the mSIRS score more than $2$ with a cutoff value of $850$ pg/mL, and sensitivity $75\%$ and specificity $79\%$ for the mSIRS score of $3$ with a cutoff value of $6000$ pg/mL ($n = 56$) (Fig. 4).
Discussion

This study shows that serum TARC measurement in patients at an early stage of a drug eruption can predict the maximal grade of systemic inflammation regardless of the type of drug eruption: DRESS/DIHS, MPE, or EM. The serum TARC levels were found to significantly correlate with all indicators of systemic inflammation—the NLR, GPS, and mSIRS score—when serum TARC levels were measured at the first consultation in our department. Among these three scores, mSIRS showed the best correlation with serum TARC levels: the correlation coefficient of 0.68 (Fig. 3). The NLR, GPS, and SIRS score have been reported to be useful for predicting mortality in various diseases. The NLR helps to predict mortality and short-term outcomes in infectious diseases, acute coronary syndrome, and heart failure.4,20–22 GPS testing can predict mortality in patients with heart failure or cancer.5,6 The SIRS score can predict mortality among the patients in intensive care units.23 It was reported that worsened vital signs that are included in the SIRS score can lead to death in patients with DRESS.9 Our finding is also supported by other reports, which indicate that the serum TARC level is associated with eosinophilia in patients with drug eruptions,17 and eosinophilia is related to the SIRS score.8,24,25 In addition, a receiver-operator characteristic curve analysis revealed that serum TARC measurement had high sensitivity and specificity in predicting GPS and mSIRS score, suggesting the utility of serum TARC measurement for prognosis of systemic inflammation (Fig. 4).

Other reports have suggested that serum TARC is upregulated preferentially in patients with DRESS/DIHS, reflecting a Th2-type immune reaction in DRESS/DIHS.14–16 Even if we had analyzed only the data on groups MPE, and EM, omitting the patients with DRESS/DIHS, most of these correlations between serum TARC levels and indicators of systemic inflammation would have been validated (Supplementary Fig. 2, 3). And most of these tendencies were observed in the respective patient groups (Supplementary Fig. 4, 5).
This result suggests that these findings are robust and not strongly tied to the type of drug eruption.

The limitation of our study is that we used mSIRS scores instead of the SIRS score because we could not calculate the respiratory rate, which is needed to calculate the SIRS score. Because mSIRS scores in the patients with DRESS/DIHS were found to be significantly higher than those in the patients with MPE or EM as shown in Figure 1, the mSIRS score appears to reflect disease severity in drug eruptions. Another limitation of the study is that SJS/TEN was not included in the study because scoring system for evaluating the severity was well established and serum TARC level was known not to increase as high as DRESS/DIHS.10,14

Although we showed a correlation between serum TARC levels and indicators of systemic inflammatory condition, the mechanism underlying the increase in serum TARC levels during drug eruptions remains unclear. Furthermore, although increased serum TARC levels are also seen in atopic dermatitis,26 they do not always lead to worsened vital signs in patients with atopic dermatitis. Connections between TARC production and systemic clinical parameters have yet to be elucidated.

In conclusion, we showed that serum TARC levels significantly correlate with indicators of systemic inflammation and of disease severity among patients with drug eruptions except SJS/TEN. Our results suggest that serum TARC at an early stage of a drug eruption may be a prognostic biomarker of severity of inflammation.

Acknowledgments

This work was partly supported by Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan [H26-nanchi(nan)-ippan-081].

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2017.06.001.

Conflict of interest

The authors have no conflict of interest to declare.

Authors’ contributions

TKF and EM designed the study and wrote the manuscript. YC, HN, KH, MO and SK confirmed diagnoses and collected the peripheral-blood samples. RO conducted the laboratory tests.
References


