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Original Article

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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List of abbreviations used:
TARC, Thymus and activation-regulated chemokine; DIHS, drug-induced hypersensitivity syndrome; DRESS, Drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema; EM, erythema multiforme; NLR, neutrophil to lymphocyte ratio; GPS, Glasgow prognostic score; SIRS, systemic inflammatory response syndrome; mSIRS, modified systemic inflammatory response syndrome; WBC, white blood cell; Alb, albumin; CRP, C-reactive protein; BT, body temperature; PR, pulse rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; ROC curve, receiver-operator characteristic curve

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

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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.[1–3]

Several indicators are known as a useful scoring system for systemic inflammation, including the neutrophil-to-lymphocyte ratio (NLR),[4] Glasgow prognostic score (GPS),[5,6] and systemic inflammatory response syndrome (SIRS) score.[7,8] Especially, worsened vital signs, which are included in the SIRS score, can lead to mortality in patients with DRESS.[9] Although the scoring system for evaluating severity of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) was reported,[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.[11–13] Recently, TARC has been given a lot of attention as a potential biomarker of drug eruptions.[14–17] Serum TARC levels are elevated preferentially in patients with DRESS/DIHS,[14,15] reflecting a Th2-type immune response in these patients.[16] 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.[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.

Methods

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.[2,18] Final diagnoses were made as follows: DRESS/DIHS in 12 patients, maculopapular exanthema (MPE) in 18 patients, and erythema multiforme (EM) in 46 patients. SJS/TEN was eliminated in this study because scoring system for evaluating the severity was established.

The details of the study were fully explained to each patient or his/her guardian, and written informed consent was obtained. This study's protocol was approved by the ethics committee of Shimane University Faculty of Medicine (approval No. 1746).

Laboratory tests and evaluation of clinical scores

The following clinical parameters were evaluated in the patients during a medical examination: the white blood cell (WBC) count, neutrophil count, lymphocyte count, serum albumin (Alb) level, and C-reactive protein (CRP) level. The NLR was defined as a neutrophil count divided by lymphocyte count. GPS was evaluated in combination with cutoff values of CRP >1.0 mg/dL and Alb <3.5 g/dL, with the highest score of 2 and lowest score of 0 (Table 1). In addition, the following vital signs were evaluated during the examination in these patients: body temperature (BT), pulse rate (PR), systolic blood pressure (sBP), and diastolic blood pressure (dBP). The modified SIRS (mSIRS) score was used for evaluating the 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.

Measurement of serum TARC levels

Serum TARC levels were quantified by a chemiluminescent enzyme immunoassay using the HISCL® system (Sysmex, Hyogo, Japan) and a TARC Assay Kit (Shionogi, Osaka, Japan).[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.

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.

Results

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).

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 $P = 0.042$,

Table 1
Evaluation of Glasgow prognostic score (GPS), with highest score 2 and lowest score 0.

GPS score	0	1	2
Cut-off values	Alb ≥3.5 mg/dL and CRP ≤1.0 g/dL	Alb <3.5 mg/dL or CRP >1.0 g/dL	Alb <3.5 mg/dL and CRP >1.0 g/dL

Alb, albumin; CRP, C-reactive protein.

Table 2
Evaluation of modified systemic inflammatory response syndrome (mSIRS) score, with highest score 3 and lowest score 0.

mSIRS score	+1	+1	+1
Cut-off values	WBC count >12,000/μL or <4000/μL	BT > 38 °C or <36 °C	PR > 90/min

WBC, white blood cell; BT, body temperature; PR, pulse rate.

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