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Serum TARC levels are strongly correlated with blood eosinophil count in patients with drug eruptions

Takayoshi Komatsu-Fujii [a], Sakae Kaneko [a], Yuko Chinuki [a], Yohji Suyama [b], Masataka Ohta [a], Hiroyuki Niihara [a], Eishin Morita [a, *]

[a] Department of Dermatology, Shimane University Faculty of Medicine, Shimane, Japan
[b] Department of Laboratory Medicine, Shimane University Hospital, Shimane, Japan

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Abbreviations:
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; WBC, white blood cell; RBC, red blood cell; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; Alp, alkaline phosphatase; γ-GTP, gamma-glutamyl transpeptidase; CK, creatinine kinase; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ROC curve, receiver-operating characteristic curve; SD, standard deviation; CLEIA, chemiluminescent enzyme immunoassay

ABSTRACT

Background: This study aims to evaluate the relationship between serum thymus and activation-regulated chemokine (TARC) levels with various clinicopathological conditions in patients with drug eruptions. The value of TARC in diagnosing drug-induced hypersensitivity syndrome (DIHS) was also examined.

Methods: Study participants included 84 patients who presented with generalized eruptions suspected to be drug-related, including DIHS, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), maculopapular exanthema (MPE), erythema multiforme (EM), erythroderma, and toxicoderma. The correlation coefficients between serum TARC levels and clinical parameters in peripheral blood samples were calculated.

Results: Serum TARC levels in patients with DIHS were higher than those found in patients with SJS/TEN, MPE, EM, and toxicoderma. TARC levels had 100% sensitivity and 92.3% specificity in diagnosing DIHS, with a threshold value of 13,900 pg/mL. Serum TARC levels positively correlated with age, white blood cell (WBC) count, neutrophil count, eosinophil count, monocyte count, atypical lymphocyte (Aty-ly) count, serum blood urea nitrogen (BUN) levels, and creatinine (Cr) levels. It negatively correlated with serum total protein (TP), albumin (Alb), and estimated glomerular filtration rate (eGFR). Among these clinical parameters, blood eosinophil counts were most strongly correlated with serum TARC levels, with a correlation coefficient of 0.53.

Conclusions: Serum TARC levels are well correlated with blood eosinophil counts in patients with generalized drug eruptions, indicating that Th2-type immune reactions underlie TARC production. Serum TARC measurements also have potent diagnostic value for DIHS, with high sensitivity and specificity.

* Corresponding author. Department of Dermatology, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan.
E-mail address: emorita@med.shimane-u.ac.jp (E. Morita).
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Introduction

Drug-induced hypersensitivity syndrome (DIHS) is a severe adverse drug eruption, which has biphasic aspects of allergic reaction to a drug and immune response to reactivation of a virus such as the human herpes virus type-6 (HHV-6). The diagnostic criteria for DIHS include seven clinical features: maculopapular rash, prolonged clinical symptoms, high fever, leucocyte abnormalities, liver dysfunction, lymphadenopathy, and HHV-6 reactivation.[1] However, early diagnosis of DIHS may prove difficult, not only because diagnostic criteria include prolonged symptoms, but also because its clinical features mimic maculopapular rash-type drug reactions or eruptions due to viral infection.[1]

Recently, thymus and activation-regulated chemokine (TARC), also known as CC chemokine ligand 17, has attracted attention as a potential biomarker for DIHS diagnosis. TARC is one of the CC chemokines that stimulates CC chemokine receptor 4 (CCR4), which is expressed on type 2 helper T (Th2) lymphocytes.[2] It recruits CCR4+ Th2-polarized T lymphocytes into sites of local inflammation, leading to a Th2-type immune response.[3–5] Regulatory T cells (Tregs) are also reported to express CCR4.[6] Since patients with atopic dermatitis (AD) show increased numbers of Th2 lymphocytes, serum TARC levels correlate with disease severity in AD.[7,8] In addition, stratum corneum TARC levels correlate with severity of local skin inflammation in patients with AD.[9]

Recently, it has been reported that serum TARC levels are higher in patients with DIHS than in patients with other severe drug eruptions including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and maculopapular exanthema (MPE).[10,11] It has also been reported that serum TARC levels can be used as a disease-specific diagnostic indicator of DIHS because elevated levels are observed, especially at an early stage.[12,13] However, studies to confirm the diagnostic value of serum TARC level for DIHS among patients with various types of drug eruptions, including erythema multiforme (EM) and erythroderma, are scarce. The association of serum TARC levels with pathophysiological aspects of drug eruptions also remains unknown.

In the current study, serum TARC levels were examined in 67 patients who presented with generalized drug eruptions, including DIHS, to confirm the diagnostic value for DIHS and to investigate the relationship of TARC to various clinical and laboratory parameters. Seventeen patients with toxicoderma, arising independently from drug eruptions, were also included.

Methods

Patients

Study participants included 84 patients (2–99 years; mean age 60.7 years) who presented with generalized eruptions suspected to be drug-related at Shimane University Hospital from April 2014 to September 2015. Of the 84 patients, 36 were male (3–89 years; mean age 61.4 years), and 48 were female (2–99 years; mean age 60.1 years). The diagnoses of DIHS and SJS/TEN were performed according to appropriate clinical criteria.[1,14] The diagnosis of toxicoderma was assigned when no causal relationship to a drug was detected, although initial clinical history and symptoms were suggestive of a drug eruption. Final diagnoses were assigned as follows: DIHS, 6 patients; SJS/TEN, 5 patients; MPE, 14 patients; EM, 37 patients; erythroderma, 5 patients; and toxicoderma, 17 patients. The background profiles of these patients are presented in Table 1 and Supplementary Table 1

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

Measurement of serum TARC levels

In order to measure serum TARC levels, a chemiluminescent enzyme immunoassay (CLEIA) was conducted, utilizing the HISCL® system (Sysmex, Hyogo, Japan) with a TARC assay kit (Shionogi, Osaka, Japan).[13] Serum TARC levels were examined at first visit to our clinic and at several time points thereafter. Maximum serum TARC levels represent the value reported for each patient.

Laboratory tests

Peripheral blood testing and biochemical examination were performed during the study and results obtained within the same week. From these results, maximum TARC levels were evaluated for correlation with serum TARC levels. The following biological parameters were evaluated: white blood cell (WBC) count; neutrophil count; eosinophil count; basophil count; monocyte count; lymphocyte count; atypical lymphocyte (Aty-ly) count; red blood cell (RBC) count; haemoglobin (Hb) level; platelet count; serum total bilirubin (T-bil) level; total protein (TP) level; albumin (Alb) level; aspartate aminotransferase (AST) level; alanine aminotransferase (ALT) level; lactate dehydrogenase (LDH) level; alkaline phosphatase (Alp) level; gamma-glutamyl transpeptidase (γ-GTP) level; creatinine kinase (CK) level; blood urea nitrogen (BUN) level; creatinine (Cr) level; C-reactive protein (CRP) level; total IgE level; and estimated glomerular filtration rate (eGFR). The eGFR was calculated according to the following equations, which were proposed for estimating renal function of Japanese patients: $194 \times Cr^{-1.094} \times Age^{-0.287}$ for male patients; $194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ for female patients.[15]

Data analysis

Unless otherwise indicated, data are presented as mean ± standard deviation (SD). Statistical analysis was conducted with SPSS software (version 22, Chicago, IL, USA). The Mann–Whitney *U*-test was used for analysis between two groups. The Spearman's rank correlation test was used for analysis of correlation. Results were considered significant when $^{*}P < 0.05$, $^{**}P < 0.02$ and $^{***}P < 0.002$.

Table 1
Background of the patients ($n = 84$).

	DIHS	SJS/TEN	MPE	EM	Erythroderma	Toxicoderma
n	6	5	14	37	5	17
TARC (pg/mL)	31,713.8 ± 28,310.7	4702 ± 3582.1	5822.5 ± 9990.4	3748.6 ± 6561.9	11,605.5 ± 7341.9	1209.7 ± 1186.8
Age (years)	76.0 ± 13.3	68.0 ± 24.0	53.7 ± 20.8	62.8 ± 22.4	69.0 ± 11.9	52.3 ± 26.7
Time lag of TARC measurement after onset (days)	11.6 ± 5.0 ($n = 5$)	11.0 ± 12.0 ($n = 5$)	5.5 ± 8.5 ($n = 13$)	7.9 ± 9.5 ($n = 34$)	8.0 ± 5.7 ($n = 2$)	8.0 ± 11.3 ($n = 17$)

Data are presented as mean ± standard deviation (SD). DIHS, drug-induced hypersensitivity syndrome; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema; EM, erythema multiforme. TARC, thymus and activation-regulated chemokine.

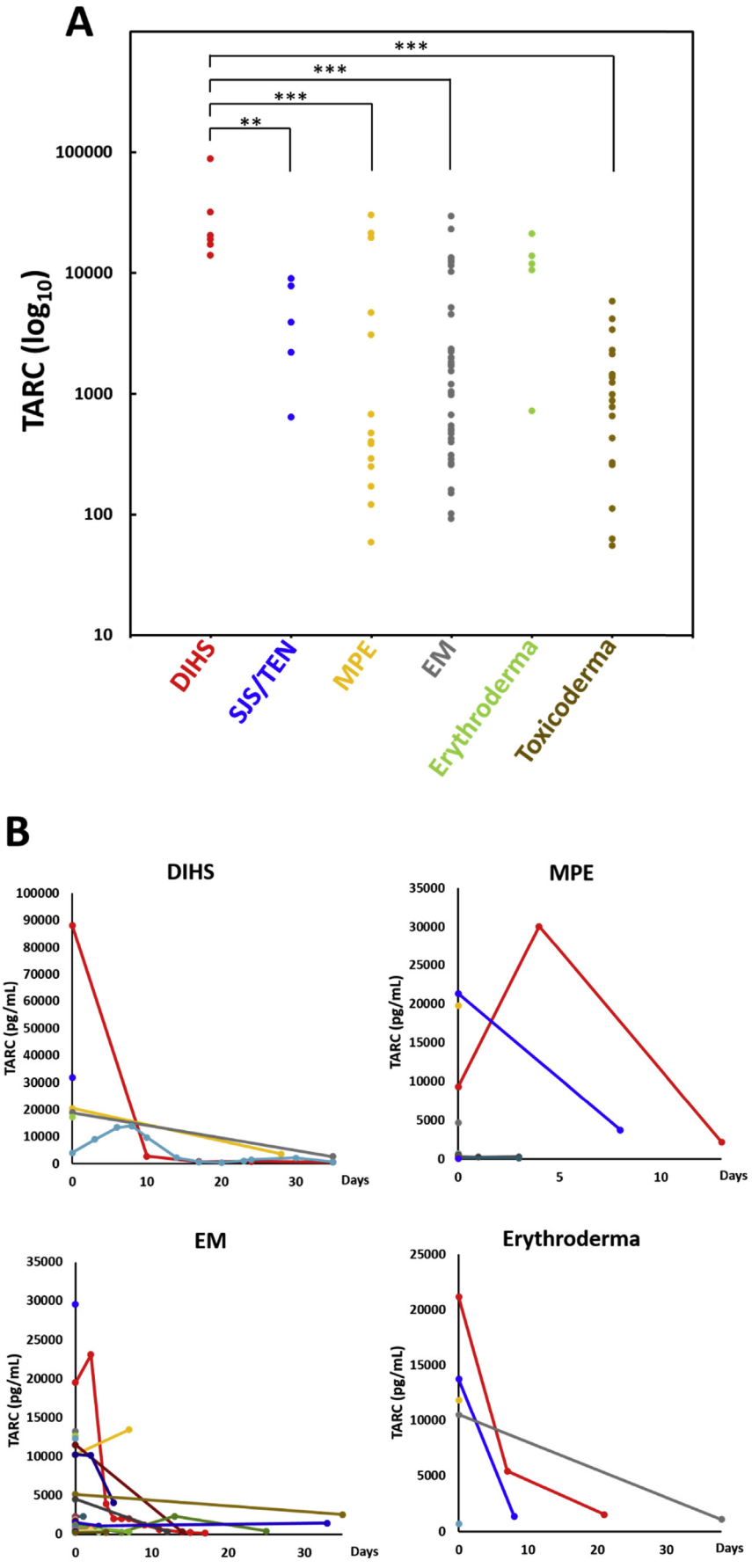

Fig. 1. (**A**) Serum TARC levels in the groups divided according to final diagnosis ($n = 84$). The results were considered to be statistically significant when $^{**}P < 0.02$, and $^{***}P < 0.002$ in Mann–Whitney *U*-test. (**B**) Time-course of serum TARC levels of the patients with DIHS, MPE, EM, and erythroderma were presented. The day of consultation was set to be day 0 in the figure.

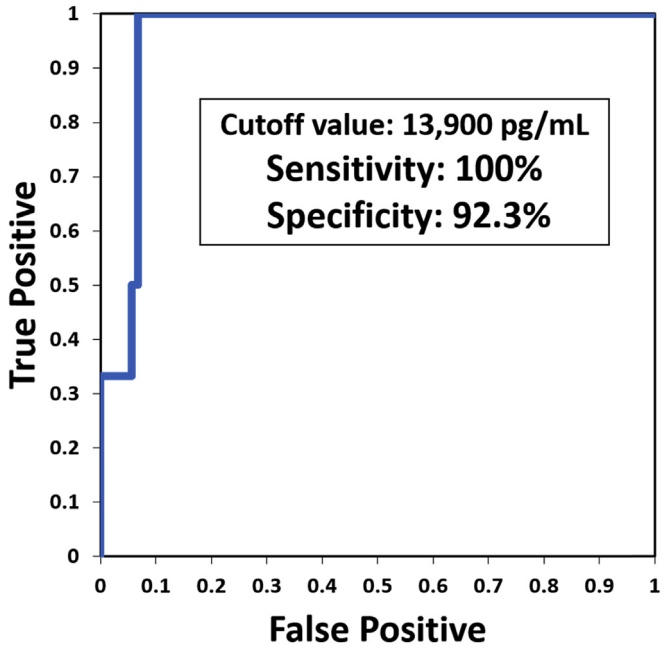

Fig. 2. Receiver operating characteristic (ROC) curve in diagnosing DIHS ($n = 84$).

Results

Serum TARC levels in patient groups stratified by diagnosis

Mean serum TARC levels in patients grouped according to final diagnosis were as follows: patients with DIHS, 31,713.8 ± 28,310.7 pg/mL; SJS/TEN, 4702 ± 3582.1 pg/mL; MPE, 5822.5 ± 9990.4 pg/mL; EM, 3748.6 ± 6561.9 pg/mL; erythroderma 11,605.5 ± 7341.9 pg/mL; and toxicoderma, 1209.7 ± 1186.8 pg/mL (Table 1). Serum TARC levels in patients with DIHS were significantly higher than patients with SJS/TEN, MPE, EM and toxicoderma (Fig. 1A). The mean time-lag of TARC measurement after onset was as follows: patients with DIHS, 11.6 ± 5.0 days; SJS/TEN, 11.0 ± 12.0 days; MPE, 5.5 ± 8.5 days; EM, 7.9 ± 9.5 days;

Table 3
Correlation between serum TARC level and respective clinicopathological parameters ($n = 84$).

Variables	Correlation coefficients	P
Age	0.38	<0.001***
WBCs	0.26	0.012**
Neutrophils	0.21	0.045*
Eosinophils	0.53	<0.001***
Basophils	0.15	0.153
Monocytes	0.26	0.015**
Lymphocytes	−0.09	0.385
Atypical lymphocytes	0.25	0.019**
RBCs	−0.14	0.183
Haemoglobin	−0.12	0.282
Platelets	0.01	0.94
TP	−0.30	0.004**
Alb	−0.43	<0.001***
Total bilirubin	−0.10	0.374
AST	0.06	0.601
ALT	0.02	0.887
LDH	0.16	0.126
Alp	0.00	0.984
γ-GTP	0.06	0.643
CK	−0.07	0.567
BUN	0.40	<0.001***
Cr	0.31	0.003**
CRP	0.08	0.484
IgE	0.24	0.098
eGFR	−0.44	<0.001***

The results were considered to be statistically significant when $^{*}P < 0.05$, $^{**}P < 0.02$, and $^{***}P < 0.002$ in Spearman's rank correlation test. WBC, white blood cell; RBC, red blood cell; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; Alp, alkaline phosphatase; γ-GTP, gamma-glutamyl transpeptidase; CK, creatinine kinase; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.

Table 2
Summary statistics of clinicopathological parameters according to final diagnosis ($n = 84$).

	DIHS ($n = 6$)	SJS/TEN ($n = 5$)	MPE ($n = 14$)	EM ($n = 37$)	Erythroderma ($n = 5$)	Toxicoderma ($n = 17$)
WBCs (/μL)	10,080.0 ± 3782.7	9476.0 ± 3320.8	7576.4 ± 3619.5	7285.0 ± 3090.7	11,390.0 ± 2278.2	8385.0 ± 3884.8
Neutrophils (/μL)	6642.0 ± 1985.8	7019.7 ± 3379.9	5064.0 ± 3719.8	4937.9 ± 2968.4	9611.7 ± 3274.7	5957.4 ± 3128.6
Eosinophils (/μL)	1816.7 ± 1096.7	1153.6 ± 1723.5	470.5 ± 660.6	629.8 ± 850.4	625.5 ± 518.1	379.4 ± 483.8
Basophils (/μL)	74.7 ± 24.2	94.5 ± 53.5	27.6 ± 20.1	35.9 ± 30.5	44.9 ± 30.4	38.4 ± 21.6
Monocytes (/μL)	1023.4 ± 1344.3	626.2 ± 274.1	478.2 ± 214.7	469.4 ± 249.2	462.0 ± 179.0	540.3 ± 303.1
Lymphocytes (/μL)	1442.5 ± 1044.1	1961.4 ± 525.6	1571.0 ± 652.5	1533.2 ± 687.6	1507.4 ± 613.6	1808.6 ± 1734.1
Atypical lymphocytes (/μL)	129.8 ± 192.8	23.6 ± 52.8	84.9 ± 235.6	37.1 ± 94.8	35.6 ± 61.7	16.1 ± 33.1
RBCs ($\times 10^6$/μL)	3.89 ± 0.41	4.21 ± 0.49	4.38 ± 0.49	4.17 ± 0.63	4.14 ± 0.43	4.67 ± 2.33
Haemoglobin (g/dL)	11.78 ± 1.1	12.8 ± 1.6	13.1 ± 1.1	12.6 ± 1.98	12.2 ± 1.86	13.8 ± 6.9
Platelets ($\times 10^3$/μL)	334.0 ± 66.1	321.4 ± 31.1	268.8 ± 104.2	245.2 ± 85.2	329.2 ± 131.0	268.9 ± 85.4
TP (g/dL)	5.90 ± 1.74	5.85 ± 1.14	5.99 ± 0.88	6.73 ± 0.74	6.38 ± 1.25	6.23 ± 1.03
Alb (g/dL)	2.60 ± 1.09	2.85 ± 0.87	3.40 ± 0.84	3.57 ± 0.64	3.03 ± 1.04	3.21 ± 0.61
Total bilirubin (mg/dL)	0.50 ± 0.23	0.55 ± 0.33	0.70 ± 0.36	1.42 ± 4.07	0.58 ± 0.13	1.42 ± 2.24
AST (U/L)	89.5 ± 114.5	40.2 ± 22.7	37.1 ± 23.6	35.1 ± 41.7	37.6 ± 25.6	42.3 ± 36.0
ALT (U/L)	110.8 ± 161.4	50.7 ± 39.0	45.6 ± 50.3	37.9 ± 45.6	35.0 ± 14.2	36.6 ± 29.3
LDH (U/L)	323.6 ± 107.7	304.7 ± 85.1	257.0 ± 64.5	308.9 ± 211.1	356.0 ± 81.66	264.1 ± 98.3
Alp (U/L)	307.2 ± 238.3	259.0 ± 249.6	205.1 ± 59.6	295.8 ± 242.6	224.0 ± 2.83	300.6 ± 254.9
γ−GTP (U/L)	152.2 ± 263.4	88.7 ± 64.4	88.7 ± 133.8	55.1 ± 76.0	34.4 ± 39.2	75.9 ± 106.3
CK (U/L)	36.2 ± 11.3	33.2 ± 29.6	52.5 ± 31.3	68.5 ± 43.4	86.2 ± 45.6	136.3 ± 198.7
BUN (mg/dL)	23.5 ± 10.1	33.0 ± 36.3	21.3 ± 19.7	18.1 ± 10.5	26.7 ± 14.2	15.9 ± 7.6
Cr (g/dL)	1.06 ± 0.38	2.15 ± 3.13	1.02 ± 1.13	0.81 ± 0.43	1.30 ± 0.69	0.72 ± 0.29
CRP (g/dL)	4.01 ± 3.42	7.60 ± 4.67	4.45 ± 5.24	3.05 ± 3.41	2.14 ± 2.09	4.14 ± 4.29
IgE (IU/mL)	164.6 ± 145.4	3128.5 ± 5927.1	178.7 ± 283.8	771.0 ± 1338.8	2960.0 ± 4220.1	272.2 ± 332.1
eGFR (mL/min/BSA)	54.6 ± 23.1	64.3 ± 41.9	69.36 ± 24.7	76.4 ± 29.6	47.7 ± 16.4	79.7 ± 32.2

Data are presented as mean ± standard deviation (SD). DIHS, drug-induced hypersensitivity syndrome; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema; EM, erythema multiforme. WBC, white blood cell; RBC, red blood cell; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; Alp, alkaline phosphatase; γ-GTP, gamma-glutamyl transpeptidase; CK, creatinine kinase; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

erythroderma 8.0 ± 5.7 days; and toxicoderma, 8.0 ± 11.3 days (Table 1). The time-course of serum TARC levels in patients with DIHS, MPE, EM and erythroderma are shown in Figure 1B.

To assess the value of serum TARC measurements for diagnosing DIHS, a receiver-operating characteristic (ROC) curve analysis was conducted with a cut-off value of 13,900 pg/mL (n = 84). Serum TARC measurements were found to have a sensitivity of 100% (6/6 patients) and a specificity of 92.3% (72/78 patients) (Fig. 2).

Correlation of serum TARC levels with clinical parameters

Mean values of respective laboratory tests are presented in Table 2. Serum TARC levels positively correlated with age, WBC count, neutrophil count, eosinophil count, monocyte count, Aty-ly count, serum BUN level and Cr level (Table 3). However, serum TARC negatively correlated with serum TP level, Alb level and eGFR (Table 3). Among these clinical parameters, blood eosinophil counts

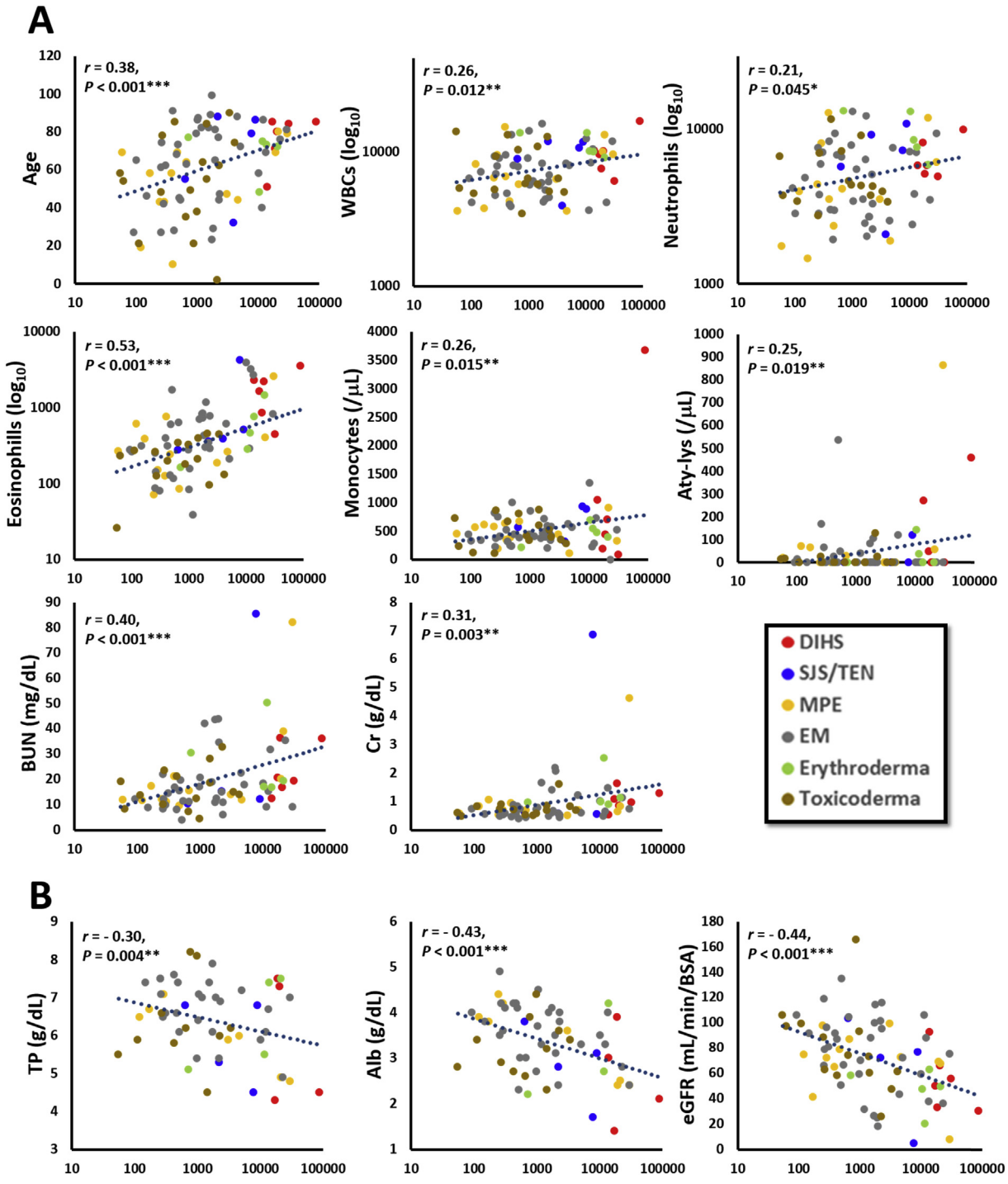

Fig. 3. (**A**) Clinicopathological parameters that are positively correlated with serum TARC level. (**B**) Negatively correlated with serum TARC level (n = 84). Explanatory variables of respective scatter plots were all serum TARC level ($\log_{10}$). The results were considered to be statistically significant when $^{*}P < 0.05$, $^{**}P < 0.02$, and $^{***}P < 0.002$ in Spearman's rank correlation test.

were most strongly correlated with serum TARC levels with the highest correlation coefficient of 0.53. However, no statistically significant correlation was observed between serum TARC levels and blood basophil count, lymphocyte count, RBC count, haemoglobin level, platelet count, serum T-bil level, AST level, ALT level, LDH level, Alp level, γ-GTP level, CK level, CRP level, or total IgE level. Graphical representation of these correlations is shown in scatter plots (Fig. 3A, B).

Discussion

The present study demonstrates that serum TARC levels are highly correlated with blood eosinophil count (correlation coefficient 0.53) in the patients studied. Our findings are consistent with previous reports that indicate serum TARC levels in patients with DIHS are significantly higher than those in patients with SJS/TEN and MPE.[10,12] ROC curve analysis revealed the value of serum TARC measurement in diagnosing DIHS with high sensitivity (100%) and specificity (92.3%) at a cut-off value of 13,900 pg/mL. These results support previous results that indicate serum TARC levels can be a unique diagnostic marker of DIHS.[12,13] In addition, 3/14 (21.4%) patients with MPE, 2/37 (5.4%) patients with EM, and 1/5 (20%) patients with erythroderma also had serum TARC levels over 13,900 pg/mL. These results indicate that these conditions share some common pathophysiological aspects with DIHS.

Since DIHS is known to share similar characteristics with a condition referred to as drug reaction with eosinophilia and systemic symptoms (DRESS), which is characterized by blood eosinophilia and organ damage,[16] it is likely that our patients with MPE, EM, and erythroderma fulfil the diagnostic criteria for DRESS. In fact, four of these six (66.7%) patients showed scores higher than 4 when applying the scoring system for classifying DRESS,[17] indicating probable (definite) cases of DRESS.

Our results are partly consistent with a past report indicating a Th-2 type immune reaction in patients with DIHS.[18] We further conclude that regardless of type of drug eruption, serum TARC levels reflect an inflammatory condition of drug eruption which results in eosinophilia and is probably driven by Th-2 lymphocyte activation.

Another important finding of the present study is that serum TARC levels positively correlate with BUN and Cr and negatively correlate with eGFR. These data indicate that serum TARC is a good indicator of renal failure in patients with drug eruptions. It is intriguing that serum TARC correlates well with patient age, and negatively with serum TP and Alb levels. This may reflect the fact that aging or low ability for protein-synthesis tends to shift the immune environment toward Th-2 lymphocyte-dominant activation. In addition, it is likely that patients in this group tended to have a lower ability to metabolize drugs and were also taking various drugs, resulting in relatively high blood concentrations of drugs. A combination of these factors may lead to enhanced TARC production in drug eruptions.[19]

We were unable to identify the TARC-producing cells. But it was suggested that patients with MPE, SJS/TEN and EM have some common clinical features with patients with DIHS. A previous paper reported that TARC may be expressed on CD11c+ dendritic cells in the lesional dermis of patients with DIHS.[12] It is therefore plausible that dendritic cells in skin lesions of patients with MPE, SJS/TEN and EM may also produce TARC, as is the case in patients with DIHS.

This study had several limitations. Since only 84 patients were enrolled, there is a possibility that statistical significance was not fully guaranteed. In addition, although some of the pathophysiological aspects of drug eruptions were examined, it remains unknown whether elevated serum TARC levels are associated with severity of the drug eruption. In addition, the root cause of the drug eruption remains unclear.

In conclusion, serum TARC levels are well correlated with blood eosinophil counts in patients with generalized drug eruptions, indicating that Th2-type immune reactions underlie TARC production. Serum TARC level is also a good biomarker for diagnosing DIHS/DRESS when drug reactions are suspected in patients presenting with generalized rash.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2016.06.003.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

TKF, EM and YC designed the study, conducted part of the laboratory tests and wrote this article. SK, MO and HN confirmed diagnoses and collected peripheral blood samples. YS conducted part of the laboratory tests.

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