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ORIGINAL ARTICLE

Serum IFN-γ-inducible chemokines CXCL9 and CXCL10 are elevated in non-immediate drug hypersensitivity reactions

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Abstract

Background: The recruitment to the skin of drug-responsive T cells is responsible for the inflammatory profiles of non-immediate drug hypersensitivity reactions (niDHRs). Maculopapular exanthema (MPE) and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) have quite distinct T cell infiltrating patterns.

Objective: To investigate serum levels of CXCL9, CXCL10 and IFN-γ in patients with niDHRs, including MPE and SJS/TEN, to evaluate correlations between the cytokines, and to determine whether the inflammatory factors correlate with clinical severity in patients with SJS/TEN.

Method: Twenty-four patients with SJS/TEN, 24 patients with MPE, and 24 healthy donors with good tolerance to the drugs involved in the drug reactions were recruited into the study. The modified severity-of-illness score for TEN (SCORTEN) and detachment of body surface area (dBSA) were used to assess the clinical severity of SJS/TEN. Serum levels of CXCL9, CXCL10 and IFN-γ were determined by ELISA.

Results: The niDHRs group, SJS/TEN and MPE subgroups all exhibited significantly higher levels of CXCL9, CXCL10 and IFN-γ compared with the control group ($P < 0.001$). Serum IFN-γ levels were positively correlated with CXCL9 levels and CXCL10 levels in patients with niDHRs ($r_s = 0.576$, $r_s = 0.449$, $P < 0.05$). None of the levels of CXCL9, CXCL10 and IFN-γ had any correlation with modified SCOTEN index or dBSA in SJS/TEN group.

Conclusions: The results suggest Th1 cytokine IFN-γ and chemokines CXCL9 and CXCL10 may play roles in the pathogenesis of niDHRs.

Keywords: Non-immediate drug hypersensitivity reactions; Stevens-Johnson syndrome; Toxic epidermal necrolysis; Maculopapular exanthema; Chemokines; CXCL9; CXCL10; IFN-γ

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Introduction

Drug hypersensitivity reactions (DHRs) are adverse events that result from specific immunological mechanisms to drugs or to their metabolites.[1,2] Drug hypersensitivity reactions can be classified into two main groups according to the time of manifestation after drug intake: immediate reactions, which occur within 60 min after drug administration and are mainly IgE-mediated, and non-immediate drug hypersensitivity reactions (niDHRs) appearing after 1 h and are mainly T-cell mediated. Skin manifestations are the most frequent drug-induced hypersensitivity reactions, with a variety of clinical manifestations ranging from immediate urticaria, to other symptoms exclusive to non-immediate reactions.[3] Maculopapular exanthema (MPE) is the most common form of niDHR, whereas Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the most severe, life-threatening niDHRs.[4] SJS and TEN are considered a spectrum of the same disorder, differing only by the degree of epidermal detachment.[5]

Until now, the pathogenesis of niDHRs has not been fully understood, but the recruitment of drug-responsive T cells to the skin is recognized to be involved.[6] It is well known that important differences of effector T cells exist between MPE and SJS/TEN, which result in diverse clinical manifestations.[7,8] In MPE, a mononuclear cell infiltrate can be found in the perivascular dermis, with T lymphocytes, mainly $CD4^+$ T cells, with the presence of neutrophils and occasionally eosinophils.[9] However, SJS/TEN is predominated by $CD4^+$ T cells infiltrating in the dermis, but $CD8^+$ T cells both in the epidermis and dermoepidermal junction.[10,11] It is believed that chemokines contribute to lymphocyte extravasation, localization and retention within inflamed tissues,[12] so we hypothesize that they play a crucial role in the recruitment of T cells in the pathogenesis of niDHRs and the course of migration of the activated T cells should be explored in the process of niDHRs. In our previous study, serum thymus activation-regulated chemokine (TARC), cutaneous T-cell-attracting chemokine (CTACK) and interleukin-10 were found to have different aspects in diverse niDHRs,[13] yet we speculate whether other chemokines are involved. We found that CTACK had a positive correlation with the detachment of body surface area in patients with SJS/TEN, but the question remains, what about other chemokines in evaluating the severity of SJS/TEN?

CXCL9 (formerly known as monokine induced by IFN-γ, mig) and CXCL10 (formerly known as IFN-γ-inducible protein-10, IP-10) are two members of the CXC subfamily of chemokines and specifically attract activated T cells expressing the chemokine receptor CXCR3.[14,15] It has been demonstrated that CXCL9 and CXCL10 play critical roles in enhancing the recruitment and activation of Th1 and Tc cells.[16,17] The production of CXCL9 and CXCL10 is specifically activated by IFN-γ on different cell types.[18] CXCL9 and CXCL10 expression has been studied in various skin diseases, including psoriasis and atopic dermatitis, but few studies concerning CXCL 9 and CXCL10 in niDHRs have been carried out.[9,19-23]

To elucidate the role of CXCL9 and CXCL10 in the mechanisms of niDHRs and evaluate their effects in diverse niDHRs, we assessed the serum levels of CXCL9, CXCL10 and IFN-γ in patients with MPE and patients with SJS/TEN in this study.

Methods

Patients and controls

From January 2013 to June 2014, patients with SJS/TEN and sex- and age-matched patients with MPE were enrolled into the study. All patients were visiting the Department of Dermatology, The First Affiliated Hospital, Sun Yat-sen University, for consultation of their skin problems. All patients enrolled in the study applied only one suspected drug during the latent period. The most probable culprit drug was identified according to the definition of adverse drug reactions provided by the World Health Organization.[24] All symptoms appeared at least 24 hours after drug administration and were alleviated after withdrawal from the culprit drugs. The diagnosis of SJS/TEN was based on clinical manifestations: fever, involvement of the mucous membranes, purpuric macules or typical targets on the face and trunk, and extent of the epidermal detachment, as follows: SJS, detachment less than 10% of body surface area (BSA); TEN, detachment greater than 30% of BSA; the severity between these two is categorized as SJS/TEN overlap. The skin develops the Nikolsky sign, whereby gentle lateral pressure causes the epidermis to slide over the basal layer. MPE consisted of itching erythematous macules or papules, often symmetric and typically polymorphous, with diffuse distribution on the face, trunk and extremities. Patients enrolled in the study were at first diagnosis and had not used systemic corticosteroids or immunosuppressive drugs to treat the underlying diseases and any drug-induced reactions. Patients who had positive serologic results for human immunodeficiency virus were excluded. None of the patients had any histories of allergic, cutaneous or rheumatoid diseases.

Sex- and age-matched healthy subjects with good tolerance to the drugs involved in the reactions were selected as controls. None of the controls had a history of DHRs nor did they have any cutaneous or immunologic diseases at the time of selection.

All procedures in this study were approved by the ethics committee of The First Affiliated Hospital of Sun Yat-sen University (no. [2012]017). Informed written consent was obtained from patients and controls.

Clinical assessment for SJS/TEN

The severity-of-illness score for TEN (SCORTEN) was modified to assess the clinical severity of SJS/TEN. The modified SCORTEN scale allots 1 point for each of the 5 variables: (1) epidermal detachment > 10% of BSA on day 1; (2) heart rate > 120 beats per minute; (3) blood urea nitrogen > 28mg/dL; (4) glucose > 252mg/dL; and (5) bicarbonate < 20mEq/L. Detachment of body surface area (dBSA) was recorded and the patient's palm can serve a reference point roughly equivalent to 1% of the BSA.

Sample collection

Serum specimens were obtained from the clotted blood of each patient at the initial diagnosis and before the introduction of treatment, as well as from controls; samples were centrifuged at 4° and 2,500 rpm for 10 minutes and then stored at -80° until tested.

ELISA for CXCL9, CXCL10 and IFN-γ

Serum levels of CXCL9, CXCL10 and IFN-γ were measured using specific ELISA kits purchased from R&D Systems, Inc. (Minneapolis, MN, USA) according to the manufacturer's protocol.

Statistical Analysis

The Wilcoxon-Mann-Whitney nonparametric test was used to compare the levels of CXCL9, CXCL10 and IFN-γ. Correlation coefficients between various parameters were assessed using the Spearman rank correlation test. *P* values lower than 0.05 were considered to indicate a statistically significant difference or correlation.

Table 1. The demographic and clinical characteristics of patients with nonimmediate drug hypersensitivity reactions and control group

Group	SJS/TEN			MPE	Controls
Subgroup	SJS	SJS/TEN overlap	TEN		
No.	11	7	6	24	24
Median age (range) (yr)	40 (18-72)			40 (19-71)	41 (18-72)
Sex M/F	11/13			11/13	11/13
Modified SCOREDN (mean ± SD)	1.3 ± 0.6	2.4 ± 0.8	3.5 ± 1.0	n/a	n/a
dBSA (mean ± SD) (%)	6.4 ± 1.9	20 ± 3.1	45.7 ± 10.6	n/a	n/a
Outcome (No.)	A (11)	A (7)	A (5), D (1)	A (24)	A (24)

Abbreviations: A, alive; D, dead; MPE, maculopapular exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; SCORTEN, the severity-of-illness score for TEN; dBSA, detachment of body surface area; n/a, not available.

Figure 1. Serum levels of CXCL9 in patients with niDHRs (n = 48), SJS/TEN (n = 24) and MPE (n = 24), and in normal control group (n = 24). niDHRs, nonimmediate drug hypersensitivity reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema.**$P < 0.001$.

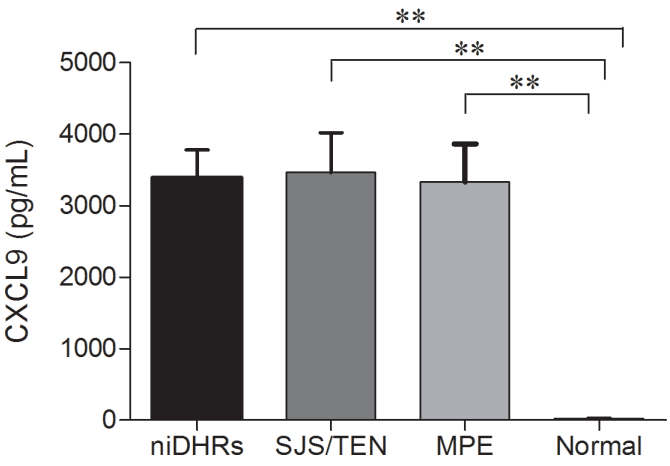


Table 2. The culprit drugs of patients with nonimmediate drug hypersensitivity reactions

	Group (No.)	
Culprit drugs	SJS/TEN	MPE
Cephalosporins	1	**6**
Amoxicillin	2	2
Fluoroquinolones	1	4
Macrolides	0	2
Clindamycin	0	1
Oxcarbazepine	2	0
Allopurinol	**8**	2
Carbamazepine	**8**	1
TCM	2	2
Phenobarbital	0	1
Methimazole	0	1
Tetanus antitoxin	0	1
Meglumine diatrizoate	0	1

Abbreviations: MPE, maculopapular exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TCM, traditional Chinese medicine.

Results

Demographics of patients and drugs implicated in niDHRs

A total of 48 patients with niDHRs were enrolled into the study. There were 24 patients with SJS/TEN including 11 patients with SJS, 7 patients with SJS/TEN overlap and 6 patients with TEN, and 24 patients with drug-induced MPE. The control group included 24 individuals. The demographic and clinical characteristics of patients and controls are shown in **Table 1**. The drugs implicated in niDHRs were listed in **Table 2**. Among the culprit drugs, allopurinol (n = 8) and carbamazepine (n = 8) were the most commonly reported to cause SJS/TEN. However, the most commonly implicated drug for MPE was cephalosporins (n = 6).

Serum CXCL9 and CXCL10 levels in niDHRs

Patients with niDHRs showed significantly higher CXCL9 levels (mean 3393.31 pg/mL) than normal controls (mean 23.75 pg/mL, $P < 0.001$; **Figure 1**). Also, as shown in **Figure 1**, CXCL9 levels were significantly higher in SJS/TEN (mean 3461.06 pg/mL) and MPE (mean 3325.55 pg/mL) in contrast to normal controls ($P < 0.001$, respectively). Similar to CXCL9, CXCL10 levels were found to be significantly increased in niDHRs than those in the normal control subjects (mean 393.49 pg/mL vs. 15.81 pg/mL, $P < 0.001$; **Figure 2**). Both SJS/TEN and MPE patients exhibited significantly higher CXCL10 serum levels than the normal control subjects (mean 403.28 pg/mL and 383.70 pg/mL vs. 15.81 pg/mL, $P < 0.001$, respectively; **Figure 2**). No difference in CXCL9 levels nor CXCL 10 levels was found between the SJS/TEN group and the MPE group ($P = 0.902$, $P = 0.099$).

Figure 2. Serum levels of CXCL10 in patients with niDHRs (n = 48), SJS/TEN (n = 24) and MPE (n = 24), and in normal control group (n = 24). niDHRs, nonimmediate drug hypersensitivity reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema.**$P < 0.001$.

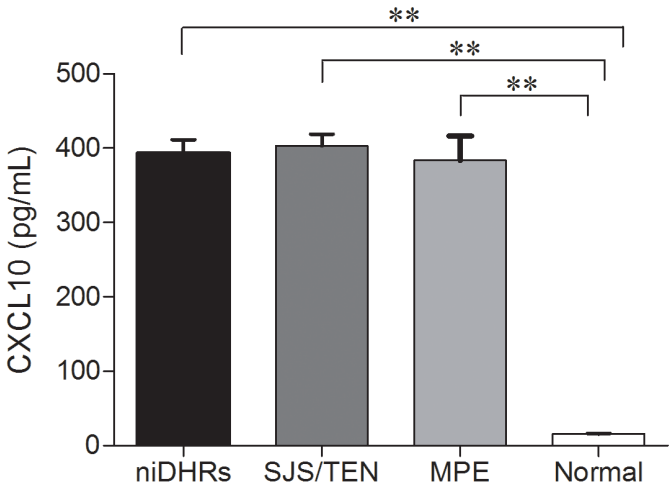
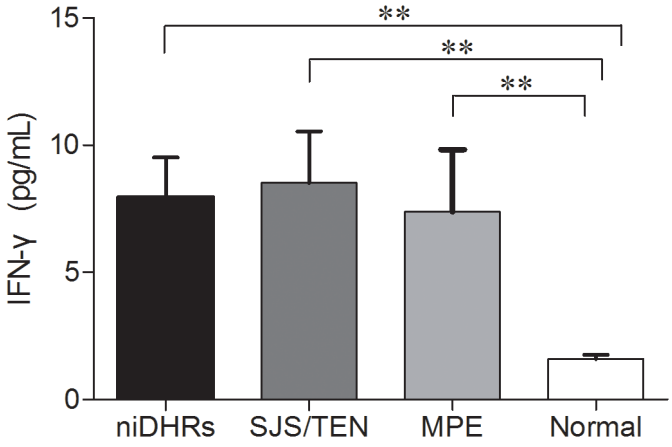


Figure 3. Serum levels of IFN-γ in patients with niDHRs (n = 48), SJS/TEN (n = 24) and MPE (n = 24), and in normal control group (n = 24). niDHRs, nonimmediate drug hypersensitivity reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema.**$P < 0.001$.



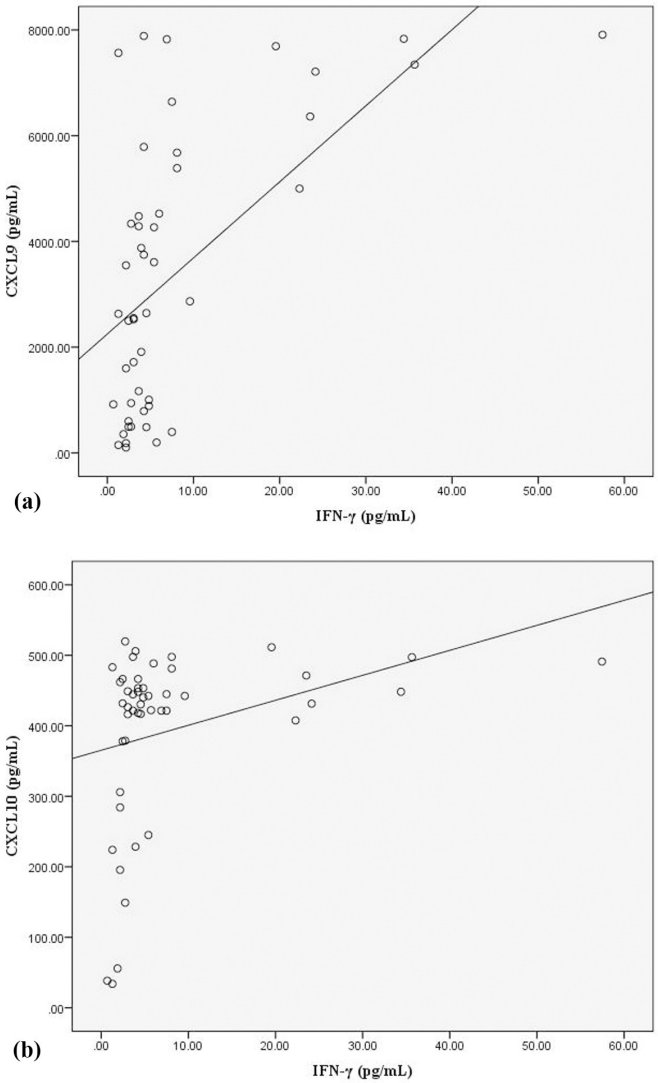
Serum IFN-γ levels in niDHRs

Serum IFN-γ levels in patients with niDHRs (mean 7.95 pg/mL) were significantly higher than those found in normal controls (mean 1.59 pg/mL, $P < 0.001$; **Figure 3**). IFN-γ levels were significantly elevated in both the SJS/TEN group (mean 8.52 pg/mL) and MPE group (mean 7.38 pg/mL) compared with the control group ($P < 0.001$, respectively; **Figure 3**). No difference in IFN-γ levels was found between SJS/TEN and MPE group ($P = 0.163$).

Correlations between serum cytokines levels in niDHRs

Serum IFN-γ levels were positively correlated with CXCL9 levels and CXCL10 levels in all 48 patients with niDHRs (r_s =0.576, r_s = 0.449, $P < 0.05$, respectively; **Figure 4a, b**). Similar positive correlations (between IFN-γ and CXCL9, IFN-γ and CXCL10) were also found in both the SJS/TEN and MPE groups (in SJS/TEN: r_s = 0.544 and r_s = 0.595, $P < 0.05$, respectively; in MPE: r_s = 0.557 and r_s = 0.569, $P < 0.05$, respectively).

Figure 4. Serum IFN-γ levels in patients with nonimmediate drug hypersensitivity reactions positively correlated with CXCL9 levels (r_s = 0.576; P < 0.05) (a) and CXCL10 levels (r_s = 0.449; P < 0.05) (b), respectively.



No correlations between serum cytokines and clinical severity in SJS/TEN

In the SJS/TEN group, none of the elevated levels of CXCL9, CXCL10 and IFN-γ showed any correlation with dBSA or modified SCORTEN index ($P = 0.63$, $P = 0.663$, $P = 0.534$ with dBSA; $P = 0.508$, $P = 0.492$, $P = 0.768$ with modified SCORTEN index).

Discussion

The current study showed that serum levels of CXCL9, CXCL10 and IFN-γ were all elevated in patients with niDHRs,

indicating the cytokines are related to the cutaneous inflammation caused by drug hypersensitivity, including both MPE and SJS/TEN.

Although discrepancies exist between authors, increasingly more studies have proved that $CD4^+$ T cells, including Th1 lymphocytes and Th2 lymphocytes, contribute to the characteristic features of MPE.[9] Our previous results showed that serum levels of TARC - a Th2 chemokine - were increased in MPE.[13] In this study, the Th1-associated cytokine IFN-γ and chemokines CXCL9 and CXCL10 were significantly elevated in untreated MPE patients. Combined with the previous study, we believe that drug-induced MPE is a mixed inflammatory pattern. Both Th1 chemoattractants, CXCL9 and CXCL10, and Th2 chemoattractant, TARC, cooperatively play roles in the development of MPE.

SJS/TEN is a disease of interest because of its life-threatening impact on patients and because the mechanisms of acute and extensive destruction of the skin are still poorly understood.[10] Cumulative evidence suggests the involvement of Th1 and Tc cells in the pathologic mechanism of SJS/TEN.[15,25,26] CD8 cytotoxic T cells are theorized to be the major inducers of keratinocyte apoptosis.[27] Th1 helper T cells can secrete IL-2 and IFN-γ and are also responsible for the activation of cytotoxic T cells.[26] Previous studies have shown that the $CXCR3^+CD8^+$ T cells subset is predominated in the peripheral blood of patients with SJS, and SJS/TEN specimens stained for immunohistochemical examination show significantly higher expression of CXCR3 than healthy control specimens.[28,29] In this study, the CXCR3 ligands - CXCL9 and CXCL10 - were found to be expressed more highly in the serum of SJS/TEN patients than in the control group. Our findings were in accordance with previous studies and supported the theory of Tc cell activation. Furthermore, the normal expression of TARC in our previous study which varied from the high expressions of CXCL9 and CXCL10 now provides further evidence of the Th1 polarization responsible for SJS/TEN.

The SCORTEN system was initially developed to assess the severity of illness and predict mortality in patients with acute SJS/TEN.[30] The scale ranges from 0 to 7 and attributes 1 point for the presence of each of 7 items. Besides the five items described in the method part, two indicators, which are age and presence of malignancy, are also included in the classic SCORTEN scale. Since age and presence of malignancy are objective and will not improve after treatment, we suggest that the two items might be excluded when assessing the dynamic severity of SJS/TEN, but that the classic SCORTEN is still valuable to evaluate the prognosis.

Although the overexpression of CXCL9 and CXCL10 was obvious in patients with SJS/TEN, the chemokines had no correlation with severity of disease. Compared with the positive correlation between CTACK and dBSA in our previous research,[13] we assume that CTACK might be more crucial and specific in the pathogenesis of drug-induced bullous exanthema and is of particular importance as an effective target for biologic agents to block to control the lethal skin condition. Nowadays, a CXCR3 antagonist is being developed for the treatment of psoriasis.[31] Since the remarkably high expression of CXCL9 and CXCL10 was presented in patients with niDHRs, there is also considerable interest in studying the use of a CXCR3 antagonist for the treatment of disease.

As we know, the identification of causative agent corresponding to DHR is valuable in the diagnosis and prevention. Enzyme-linked immunosorbent spot (ELISPOT) measuring IFN-γ has proved to be a sensitive *in vitro* method to detect culprit drugs causing niDHRs.[32] Taking our findings into account, assays focusing on IFN-γ and chemokines CXCL9 and CXCL10 induced by IFN-γ, appear to be promising to diagnose the culprit drugs related to niDHRs, both MPE and SJS/TEN included.

Taken together, our results suggest that the Th1 cytokine IFN-γ and chemokines CXCL9 and CXCL10 may be related to the development of niDHRs. Limitations of the present study include the small number of the patients related to different categories of drugs, and the lack of studies on the skin samples in order to confirm the presence and localization of the chemokines, in which we would speculate an overexpression of the chemokines in skin specimens of the patients. Nevertheless, the study might be a clue to develop ideal assays to identify culprit agents causing drug induced cutaneous reactions, and a potential treatment target.

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