ORIGINAL ARTICLE

Peripheral Blood Eosinophil Counts Predict the Prognosis of Drug Eruptions

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Abstract

Background: Previous studies indicated that eosinophils infiltrate the skin during drug eruptions and that counts may become elevated in circulation. However, little is known about the role of eosinophils in the prognosis of patients with drug eruption.
Objective: This study aims to investigate the correlation between circulating eosinophil counts and the prognosis of patients with drug eruption.
Methods: A total of 113 patients were enrolled in this study. Clinical features, peripheral blood eosinophil counts, and liver function were analyzed in patients and controls.
Results: Our study indicated that eosinophils changed dynamically in different types of drug eruption and that mean eosinophil counts in patients with erythema multiforme–type drug eruption were significantly higher than in patients with other types of eruption. Most patients with eosinophilia had poor liver function, prolonged corticosteroid use, and extended hospitalization, all of which indicate severe disease.
Conclusions: Our data suggest that circulating eosinophil counts were positively correlated with the severity of the drug eruption. Therefore, corticosteroids may be needed to treat patients with eosinophilia in clinical practice.

Key words: Drug eruptions. Prognosis. Eosinophils.

Resumen

Antecedentes: Estudios previos indican que los eosinófilos infiltran la piel durante el curso de las erupciones medicamentosas y pueden elevarse a nivel circulante. No obstante se sabe poco acerca del papel de los eosinófilos en el pronóstico de estas reacciones.
Objetivo: El objetivo de este estudio fue determinar la posible correlación entre el número de eosinófilos circulantes y el pronóstico de los pacientes con erupciones medicamentosas.
Métodos: Para ello, se estudiaron 113 pacientes afectos de estas reacciones y se analizó la clínica, se determinaron los eosinófilos circulantes y la función hepática de los mismos, así como de controles sanos.
Resultados: Los resultados de este estudio indican que el número de eosinófilos cambia en los diferentes tipos de reacciones o erupciones medicamentosas y que el porcentaje de eosinófilos en el eritema polimorfo es significativamente mayor que el que presentan los pacientes con otro tipo de eritema.
La mayoría de los pacientes con eosinofilia muestran una pobre función hepática, alto uso de corticosteriodes y hospitalización prolongada indicando la gravedad del proceso.
Conclusiones: En conclusión estos datos sugieren que los eosinófilos circulantes se correlaciona positivamente con la gravedad del cuadro clínico con necesidad de tratamiento con corticosteroides.

Palabras clave: Erupciones medicamentosas. Pronóstico. Eosinófilos.

Introduction

The skin is one of the organs most often affected by adverse drug reactions. Drug eruptions are adverse reactions of the skin to drugs. These reactions are often accompanied by severe complications, which restrict the use of the medication. Adverse drug reactions are a public health problem owing to the frequency of their occurrence.

Previous in vivo and in vitro data indicate that eosinophils are involved in drug-induced cutaneous reactions [1-3]. Histological examination of drug-induced lesions indicates that mixed inflammatory cells, including a large number of eosinophils, infiltrate the skin [1,4-6]. Additional studies indicate that drug eruptions may also be associated with increased counts of circulating eosinophils [1,7], especially in patients with drug rash with eosinophilia and systemic signs (DRESS) syndrome, which is commonly defined by rash with eosinophilia and multiorgan involvement, including increased liver enzyme levels [8,9]. Eosinophils contribute to tissue damage through the release of various toxic granule proteins, such as eosinophilic cationic protein, major basic protein, and eosinophil peroxidase [10-12]. Thus, eosinophils play a key role in drug-induced cutaneous eruptions. However, hypersensitive reactions to drugs can cause different types of skin disorders, including morbilliform rash, erythema multiforme, and urticaria. Variations in eosinophil counts in different types of drug-induced cutaneous reactions have not been fully elucidated. Additionally, the dynamic changes in eosinophils in patients with drug eruption and the ability of eosinophil counts to predict the prognosis of drug eruptions have not been investigated in detail [8].

We found that depletion of circulating eosinophils was common in most patients with drug eruption. In addition, patients with eosinophilia had poor liver function, prolonged corticosteroid use, and extended hospitalization, findings that indicate severe disease. Our data suggest that circulating eosinophil counts correlated positively with the severity of the eruption and that corticosteroids may be necessary for the treatment of patients with eosinophilia.

Methods

Study Population and Variables

This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China. All patients submitted a signed informed consent before treatment. The patients were hospitalized because of drug eruption at the Department of Dermatology in Zhongshan Hospital, Fudan University between 2007 and 2010. The diagnosis of drug eruption was based on skin lesions and suspected drug use history, and the types of drug eruption were classified according to Wintroub and Stern [13]. The study sample comprised 113 patients with a diagnosis of drug eruption. Of these, 31 were classified as morbilliform rash, 49 as erythema multiforme, and 33 as urticaria. Patient age, sex, and eosinophil counts are presented in Table 1. Five patients had drug fever, and 2 of the patients with erythema multiforme had superficial erosions of the oral mucosa. Vital signs were unaltered in all cases. The drugs responsible included amoxicillin, cephalosporins, antiepileptic agents, allopurinol, and herbs. Table 2 shows the type of eruption and the drugs involved in each. The control group comprised 23 patients with acute urticaria and no history of drug intake and 15 healthy volunteers. All 38 patients gave their informed consent. Patients with atopy and severe blood diseases were excluded from the study, as were patients with DRESS syndrome.

Blood Eosinophil Count and Detection of Liver Enzymes

Peripheral blood samples were obtained from all patients between 6 AM and 7 AM, before the corticosteroid was administered. Eosinophils, total leukocytes, lymphocytes, and basophils were counted using an automated hematology analyzer Sysmex XE-2100 (Sysmex). Eosinophil counts, expressed as absolute numbers (reference range, 0.02×10^9 to 0.5×10^9 cells/L) were recorded; absolute eosinophil counts of $\leq0.02\times10^9$ cells/L were defined as low, and counts of $>0.5\times10^9$ cells/L as high [14]. Serum levels of alanine aminotransferase (ALT; reference range, <75 U/L) and

Table 1. Characteristics of Patients

Variables	Pollen				Controls	
	Erythema Multiforme	Morbilliform	Urticaria	Total	Urticaria Controls	Healthy Controls
Age, y, mean (SD)	47.5 (19.8)	53.0 (20.0)	45.0 (16.4)	49.1 (19.0)	53.5 (18.8)	50.9 (8.3)
Sex						
Male	26	12	19	57	11	8
Female	23	19	14	56	12	7
Eosinophil counts, $\times10^9$/L						
Mean	0.28 (0.54)	0.03 (0.08)	0.06 (0.07)	0.15 (0.38)	0.13 (0.11)	0.14 (0.12)
<0.02	16	24	14	54	3	0
0.02-0.5	23	7	19	49	20	15
>0.5	10	0	0	10	0	0

Table 2. Type of Eruption and Drugs Involved

Type of Drug Eruption	Drugs
Erythema multiforme	Cefaclor, metamizole, allopurinol, paracetamol, acetylsalicylic acid, fosfomycin, norvancomycin, cefotiam, celecoxib, lamotrigine, clindamycin, antitetanic serum, levofloxacin, meloxicam, carbamazepine, Yinqiao, cefprozil, ibuprofen, aminophenazone, sodium phenobarbital, iodine, amoxicillin, cefuroxime, metronidazole, metamizole sodium.
Morbilliform	Cefaclor, astragalus, cefuroxime, metamizole, ibuprofen, cetirizine, paracetamol, metronidazole, acetylsalicylic acid, meloxicam, cefoxitin, levofloxacin lactate, ofloxacin, ampicillin, notoginseng, sorafenib, amoxicillin, tinidazole, isatis, clarithromycin.
Urticaria	Paracetamol, acipimox, cefixime, terbinafine, acetylsalicylic acid, cephalexin, pseudoephedrine hydrochloride, indomethacin, penicillin, antitetanic serum, kudzuvine root, diclofenac, vaccines, gynecologic Qian Jin tablets, heparin, cefprozil, ofloxacin, losartan, thiamazole, Ping Xiao tablets, San Huang tablets, iopromide, captopril.

aspartate aminotransferase (AST; reference range, <75 U/L) were detected the same day using an automatic chemistry analyzer (Hitachi 7170A, Hitachi).

Statistical Analysis

All statistical analyses were performed with SPSS, version 15.0 (SPSS Inc). Quantitative data are expressed as mean (SD). Statistical significance was determined using an analysis of variance followed by Bonferroni post hoc tests for comparisons of multiple means or the *t* test. The χ^2 test was used for comparisons between groups. Circulating eosinophil counts during the course of the disease in 10 patients with erythema multiforme were compared using a paired *t* test. Correlations were determined using Spearman's rank correlation. $P<.05$ was considered statistically significant.

Results

Patient Characteristics

The study sample comprised 113 patients with drug eruption, 15 healthy controls, and 23 patients with acute urticaria but no history of drug intake. No statistically significant differences were detected between the various types of drug eruption (morbilliform, erythema multiforme, and urticaria) with respect to gender ($P>.05$, Table 1). Similarly, no significant differences were found in the mean (SD) age of the patients with drug eruption (49.1 [19.0] years), healthy controls (50.9 [8.3] years, $P>.05$), and patients with acute urticaria (53.5 [18.8] years, $P>.05$, Table 1). Patients were admitted to hospital 1.44 (0.8) days after the onset of rash, although no significant differences were found between the groups (data not shown). Patients with drug eruption did not receive systemic corticosteroids before admission to hospital. After diagnosis of drug eruption, patients received corticosteroids on admission to hospital; patients also received complementary therapies, such as gastroprotective agents, antihistamines, and topical treatment. Patients with hypertension and diabetes continued their current treatments. The typical skin manifestation of erythema multiforme–type drug eruption is a central dusky purpura surrounded by a pale raised edematous ring and macular erythema. The central area may be bullous. Urticaria-type drug eruption is characterized by the appearance of wheals, which are generally surrounded by a red halo. Morbilliform drug eruption is characterized by erythema, often with small papules throughout.

Eosinophil Counts in Patients With Drug Eruption

No statistically significant differences were detected between the drug eruption group and the control group with respect to kidney function and blood levels of total leukocytes, lymphocytes, and basophils (data not shown). Neutrophilia was detected in several patients with drug eruption, although no significant differences were found between the 3 groups of drug eruption patients and the healthy controls (data not shown). Unexpectedly, the percentage of drug eruption patients with low eosinophil counts ($<0.02\times10^9$ cells/L) was significantly higher than that of controls with urticaria and healthy controls (48%, 13%, and 0%, respectively) (Figure 1, A; Table 1), although the average eosinophil counts in patients with drug eruption were not significantly different from those in the control group ($P>.05$) (Figure 1, B). Interestingly, most patients with drug eruption and high eosinophil counts (>0.5×109 cells/L) were in the erythema multiforme–type group (Figure 1, A; Table 1). We further examined whether eosinophil counts varied between the 3 types of eruption. A horizontal comparison of the 3 groups confirmed that eosinophil counts were significantly higher in patients with

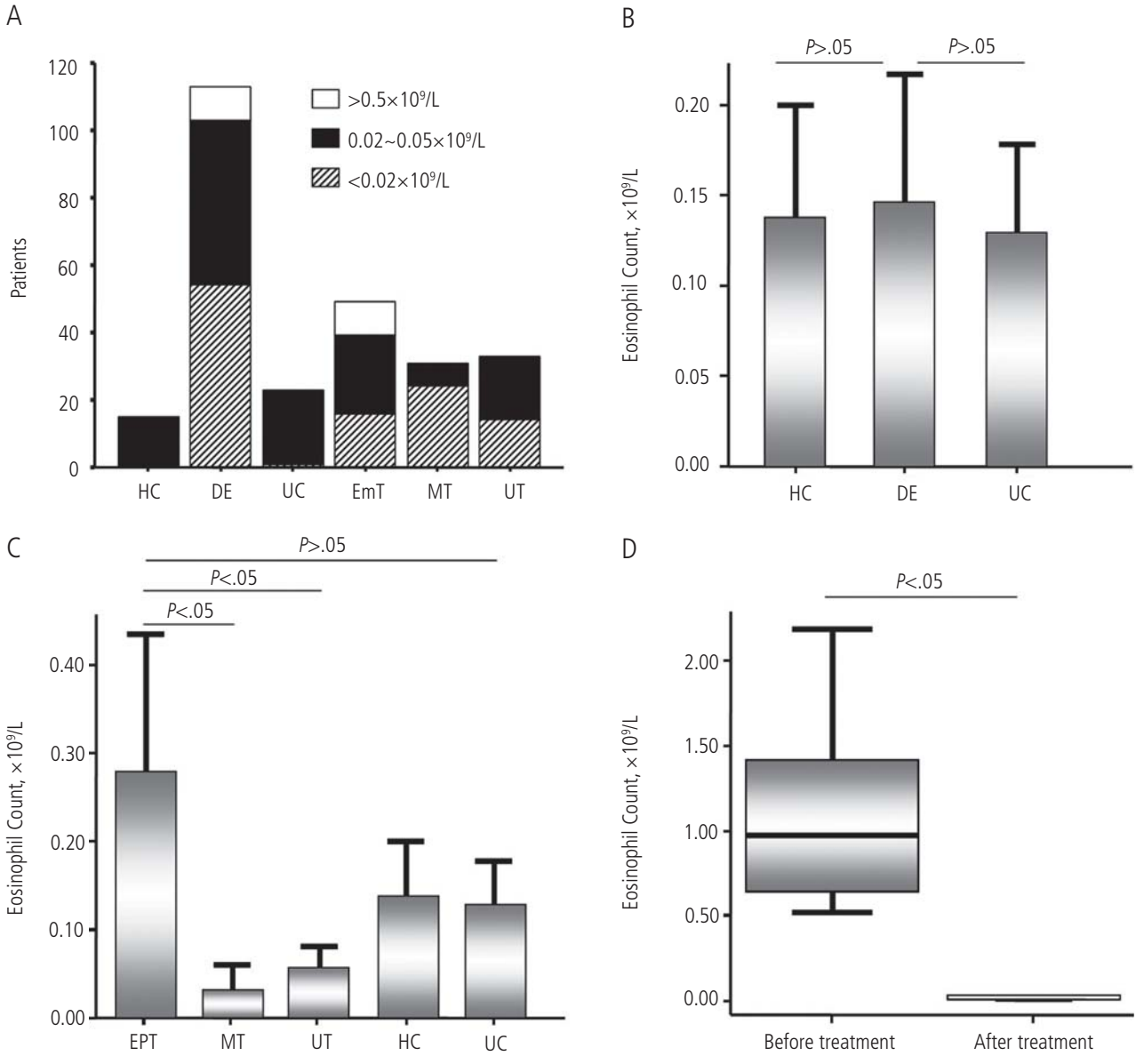

Figure 1. Eosinophil counts in patients with drug eruption. A, Percentage of individuals with eosinophil counts $<0.02\times10^9$, 0.02×10^9 ~ 0.5×10^9, $>0.5\times10^9$ cells/L. B, Average eosinophil counts in patients with drug eruption, healthy controls, and urticaria controls. C, Horizontal comparison of eosinophil counts between the different drug eruption classes. D, Longitudinal monitoring of eosinophil counts in 10 patients with drug eruption manifesting as erythema multiforme. HC indicates healthy control; DE, drug eruption; UC, urticaria control; EmT, erythema multiforme–type; UT, urticaria-type; MT, morbilliform type.

erythema multiforme–type eruption than in patients with the other types (Figure 1, C). Longitudinal analyses indicated that the increased eosinophil counts ($>0.5\times10^9$ cells/L, n=10) decreased significantly after treatment with corticosteroids in patients with erythema multiforme–type drug eruption (Figure 1, D).

Eosinophil Counts and Disease Severity

Because eosinophil counts were significantly higher in patients with erythema multiforme–type eruption than in the other classifications and most drug eruption patients with high eosinophil counts ($>0.5\times10^9$ cells/L) were in the erythema multiforme–type group (Figure 1, A and C; and Table 1), we focused on whether there was a positive relationship between eosinophil counts and disease severity in patients with erythema multiforme. Thus, we compared the average eosinophil counts with liver function (serum levels of ALT and AST), cumulative corticosteroid usage, and days of hospitalization (erythema multiforme–type patients). A positive correlation was found between eosinophil counts and serum levels of ALT and AST (Figure 2, A and B). Furthermore, eosinophil counts were

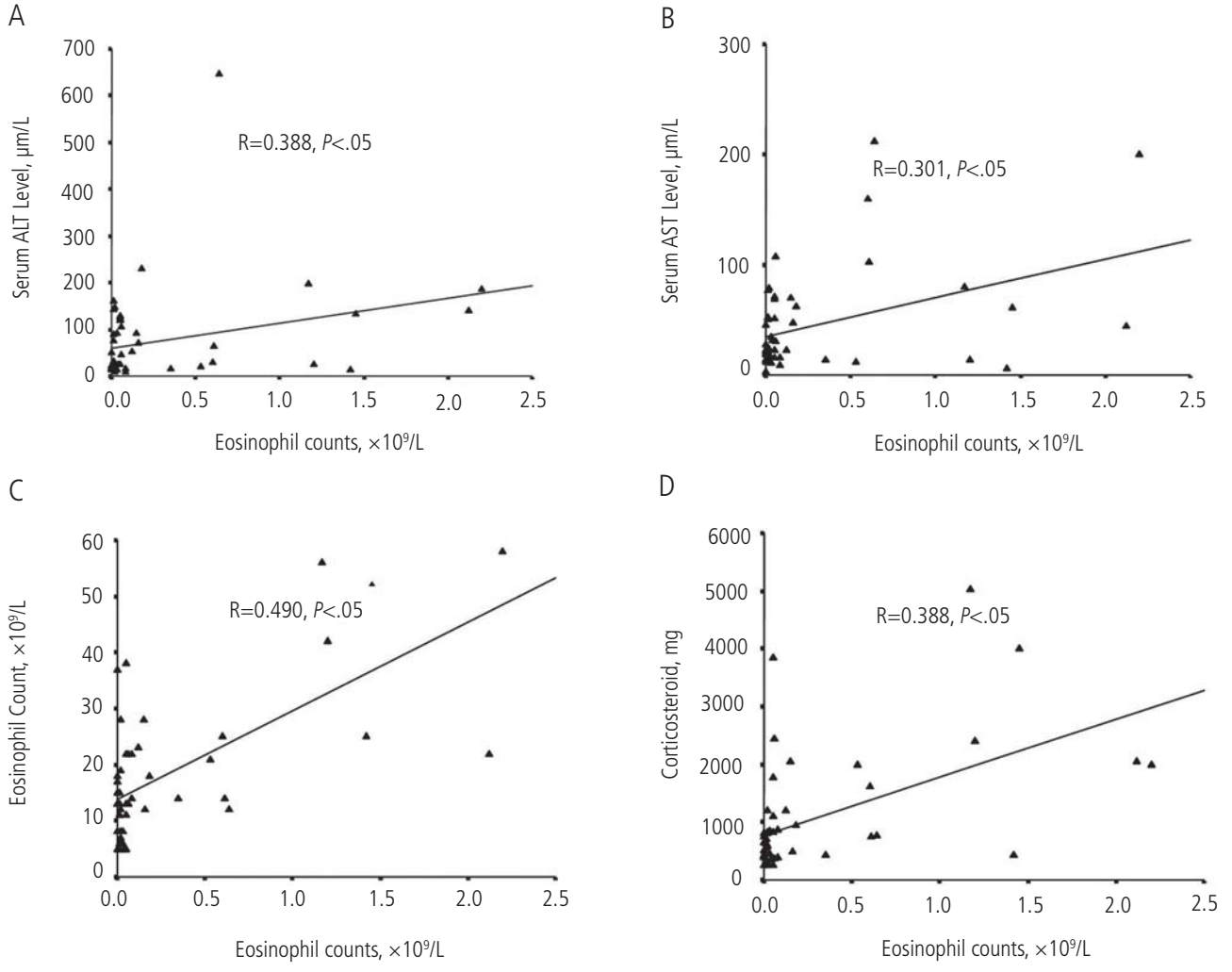

Figure 2. Eosinophil counts and disease severity were positively correlated in patients with drug eruption manifesting as erythema multiforme. Comparisons between eosinophil counts and serum ALT levels (A), serum AST levels (B), days of hospitalization (C), and cumulative corticosteroid usage (prednisone, mg) (D).

positively correlated with longer periods of hospitalization (R=0.490, *P*<.05) (Figure 2, C) and cumulative corticosteroid use (R=0.557, *P*<.05. Figure 2, D). These data indicated that circulating eosinophil levels may be closely related to disease severity in patients with erythema multiforme–type eruption. Similar results were recorded for all the study patients with drug eruption (data not shown).

We further examined the effect of low or high eosinophil counts on the prognosis of all patients with drug eruption. Because eosinophil counts between 0.02×10^9 and 0.5×10^9 cells/L were considered normal [15], patients were classified into 3 groups, as follows: group 1, $<0.02\times10^9$ cells/L (n=54); group 2, 0.02×10^9 to 0.5×10^9 cells/L (n=49); and group 3, $>0.5\times10^9$ cells/L (n=10). No differences were found between these 3 groups with respect to age (data not shown). In terms of liver function, group 3 had higher average serum ALT and AST levels than group 1 and group 2 (*P*<.05. Figure 3, A and B). In terms of mean length of stay, group 3 patients remained in hospital longer (32.7 [17.6] days) than group 1 and group 2 patients (9.8 [5.9] days and 12.0 [7.5] days, respectively, *P*<.05, Figure 3, C). Although all patients were prescribed corticosteroid treatment after diagnosis of drug eruption, we focused on the cumulative use of corticosteroids in patients with erythema multiforme–type eruption and found that the cumulative usage of corticosteroids in group 3 was much higher than in group 1 and group 2 (*P*<.05. Figure 3, D). These data suggest that eosinophil counts are highly correlated with the severity of the drug eruption and that eosinophil counts may be a promising predictor of the severity of drug eruptions.

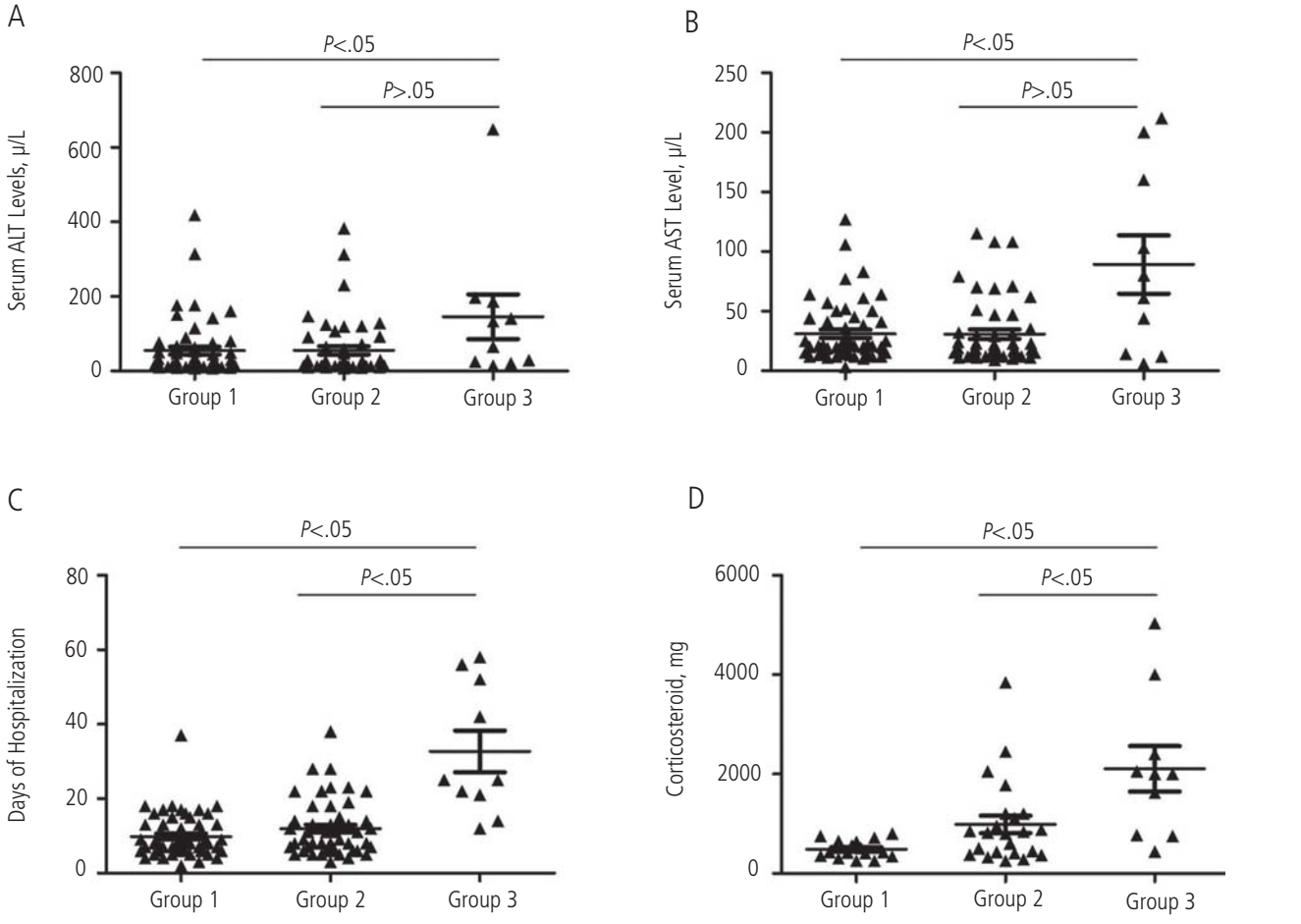

Figure 3. Role of eosinophil counts in the prognosis of drug eruption. Patients with drug eruption were classified into 3 groups according to their eosinophil counts: group 1, $<0.02\times10^9$ cells/L; group 2, 0.02×10^9 to 0.5×10^9 cells/L; and group 3, $>0.5\times10^9$ cells/L. A, Serum ALT levels. B, Serum AST levels. C, Days of hospitalization in all enrolled patients with drug eruption. D, Cumulative corticosteroid use (prednisone, mg) in patients with erythema multiforme.

Discussion

The proliferation and differentiation of eosinophils in bone marrow and their subsequent mobilization and activation are controlled by T-cell–produced cytokines, particularly interleukin (IL) 5, which is produced by a subset of type 2 helper T (T_H2) cells. Eosinophil activity is also augmented by T_H1 cytokines, including IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [11,15-18]. In general, the level of eosinophils is normally tightly regulated. In healthy controls, eosinophils account for only a small minority of peripheral blood leukocytes, and their presence in tissues is primarily limited to the gastrointestinal mucosa [19]. However, under certain conditions, eosinophils can selectively accumulate in peripheral blood or in tissue [10,20,21]. Any perturbation that results in eosinophilia, defined as an abnormal accumulation of eosinophils in blood or tissue, has profound clinical effects. Growing evidence indicates that marked accumulation of eosinophils occurs in several disorders, such as allergic diseases, parasitic infections, autoimmune diseases, inflammatory disorders, and cancer [11,19,22-28].

Although average eosinophil counts were not significantly different between patients with drug eruption and controls, the percentage of patients with low eosinophil counts was significantly higher in the drug eruption group than in the control group. Eosinophilia occurs in 4 stages: *(1)* differentiation and proliferation of eosinophils in bone marrow; *(2)* rolling, adhesion, and migration of eosinophils; *(3)* specific migration through chemoattraction; and *(4)* activation and subsequent cell death [11]. During the acute stage of drug eruption, circulating eosinophils recruited to cutaneous lesions or consumed in larger numbers than the bone marrow can immediately replenish might contribute to the low level of circulating eosinophils. The mechanism underlying eosinophil depletion in patients with drug eruption requires further investigation.

The external manifestations of drug eruption are diverse. We only focused on 3 types because of the small number of available clinical samples and time constraints. Interestingly, more patients with erythema multiforme–type drug eruption had high eosinophil counts (>0.5×10^9 cells/L) than patients from the other groups (Figure 1, A; Table 1). The high levels of circulating eosinophils in patients with erythema multiforme–type drug eruption could be due to the previously described overproduction of IL-5, IL-3, and GM-GSF in peripheral blood and lesions during drug eruption [1,2,29]. High levels of these cytokines could stimulate eosinophil differentiation and proliferation in bone marrow and enhance eosinophil recruitment to peripheral blood and lesions [15,16]. Urticaria-type drug eruption is mainly related to type I allergies and rarely involves overproduction of cytokines such as IL-5, thus potentially explaining the decrease in eosinophil counts in urticaria-type drug eruption.

Eosinophils can produce major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase, which could directly destroy involved tissue or amplify the inflammatory cascade by recruiting other effector lymphocytes into the inflammatory loci [20,22,30]. Thus, eosinophils likely play a key role in the pathogenesis of drug eruptions. Our data indicated that eosinophil counts were positively correlated with poor liver function, extended hospitalization, and prolonged corticosteroid use in patients with erythema multiforme–type drug eruption. Similar findings were recorded for urticaria-like and morbilliform drug eruption. Given the tendency toward poor liver function, extended hospitalization, and increased eosinophil counts, circulating eosinophil counts might also be a prognostic marker of drug eruption.

Eosinophil counts did not return to normal levels without systemic corticosteroids, which are the most effective agent for reducing eosinophilia [11]. Corticosteroids can suppress the transcription of a number of genes related to eosinophil growth and recruitment, including the genes for IL-3, IL-4, IL-5, GM-CSF, and various chemokines including the eotaxins [11,30]. Administration of corticosteroids can prevent the expansion of eosinophils in bone marrow and peripheral blood, block the infiltration of eosinophils into involved skin, and inhibit the tissue damage caused by eosinophils secreting various toxic granule proteins [30]. Thus, our findings could guide use of corticosteroids in clinical practice for the treatment of patients with eosinophilia.

In summary, our study indicated that depletion of circulating eosinophils was common in patients with drug eruption. However, in most patients with eosinophilia, we observed poor liver function, extended hospitalization, and prolonged cumulative corticosteroid use, all of which indicate severe disease. Therefore, corticosteroids may be necessary for the treatment of these patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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