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Study on Plasma IL-5 and sFas-L in Exanthematous Drug Eruption and Infectious Mononucleosis

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Abstract: **Objective:** Exanthematous drug eruptions(EDE) and infectious mononucleosis (IM) may both manifest with erythema, papules, and maculopapular rashes. However, the pathogenesis of the two conditions differs: EDE are mediated by hypersensitivity reactions, whereas IM is caused by viral infection. These divergent mechanisms may be reflected in distinct cytokine expression profiles during disease progression. This study aimed to identify potential cytokine-based diagnostic markers by measuring plasma levels of IL-5 and sFas-L in patients with EDE and IM. **Methods:** A total of 20 patients diagnosed with EDE, 20 patients with IM, and 20 healthy controls were recruited from the Affiliated Hospital of Chengde Medical University. Plasma levels of IL-5 and sFas-L were measured using enzyme-linked immunosorbent assay (ELISA). **Results:** Compared with the control group, plasma IL-5 concentrations were significantly elevated in both the EDE group and the IM group, with statistically significant differences ($P< 0.05$). However, the difference in IL-5 levels between the eruptive drug eruption group and the control group was not statistically significant *(*$P> 0.05$). Compared with the healthy control group, the plasma sFasL concentration was significantly elevated in the eruptive drug eruption group and the IM group, with statistical significance ($P<0.05$). However, no significant difference in sFasL levels was found between the eruptive drug eruption group and the IM group ($P> 0.05$). The IM group showed significantly higher rates of elevated peripheral blood lymphocyte counts, CK-MB, and LDH levels, as well as a greater frequency of decreased serum phosphorus (P) compared to the drug eruption group ($P<0.05$). Conversely, lymphopenia was more prevalent in the drug eruption group than in the IM group, also showing statistical significance ($P<0.05$). **Conclusion:** Plasma IL-5 levels were elevated in both conditions and thus sFas-L were not useful for differential diagnosis. Additionally, increased levels of peripheral lymphocytes, CK-MB, LDH, and decreased serum phosphorus are suggestive of IM, while lymphopenia is more indicative of drug eruption.

Keywords: Exanthematous drug eruption; Infectious mononucleosis; IL-5; sFas-L

1. Introduction

Exanthematous drug eruption(EDE)is the most common cutaneous manifestation among adverse drug reactions. Typically, generalized skin rashes appear between 6 days and 4 months after the initial administration of the drug, most commonly within 6 to 12 days. The skin lesions may present as erythema and papules, and can be accompanied by various primary lesions such as vesicles, pustules, petechiae, ecchymoses, and wheals[1]. Systemic symptoms such as fever (with body temperature reaching 38–39.8 °C) and diarrhea may also occur.

Infectious mononucleosis (IM) is an infectious disease caused by the Epstein–Barr virus (EBV). Approximately 10% to 20% of IM patients develop rashes—including erythema, papules, herpes-like lesions, petechiae, ecchymoses, and wheals—between the 4th and 10th day after the onset of fever [2]. This incidence increases significantly when penicillin-class antibiotics are administered for 7 to 8 days[2, 3]. Regardless of whether antibiotics are used, the time from disease onset to rash appearance in IM closely overlaps with the sensitization period of EDE, and the clinical presentation of the rash is often similar in both conditions.

In clinical settings, dermatologists are frequently required to differentiate rashes caused by IM from those caused by EDE. Misdiagnosing a drug-induced exanthema as a viral rash caused by EBV may result in continued drug administration, potentially leading to severe cutaneous adverse drug reactions such as toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS)[4, 5]. Conversely, if a rash caused by IM is misdiagnosed as a drug eruption, the premature discontinuation of necessary medications may exacerbate the viral infection, leading to complications such as severe pharyngeal or laryngeal edema, neurological manifestations, thrombocytopenic purpura, myocarditis, pericarditis, or prolonged disease duration with risks of splenic rupture, meningitis, and cardiac inflammation, all of which may be life-threatening.

To distinguish EBV-induced rashes from drug eruptions, dermatologists must consider factors such as the interval between drug use and rash appearance, the temporal relationship between fever and rash, the pattern of rash onset, morphological characteristics of the lesions, viral serological results, and infection-related laboratory indicators. However, the difficulty in differentiation remains high, given the similar latency periods for rash appearance in both diseases and the increased incidence of rash in IM following antibiotic use [2].

Clinically, cytokines IL-5 and sFas-L were abnormally expressed in infectious and allergic diseases[6-8]. How these cytokines are expressed in EDE and IM is unknown. This study aims to differentiate between EDE and IM by analyzing the expression levels of peripheral blood cytokines IL-5 and sFas-L in affected patients, thereby providing an immunological basis for distinguishing between erythema, papules, and maculopapular rashes caused by the two conditions.

2. Materials and methods

2.1 Case Selection

From October 2019 to December 2020, patients diagnosed with EDE and IM were recruited from the Dermatology and Pediatric outpatient clinics and inpatient wards of the Affiliated Hospital of Chengde Medical University. The study included 20 patients with exanthematous drug eruption (9 males, 11 females) and 21 patients with IM (11 males, 10 females) as the experimental group. Additionally, 20 healthy volunteers (11 males, 9 females) who met the inclusion criteria for healthy controls were recruited from the hospital's Physical Examination Center to form the control group.

Participants were categorized into three groups: the EDE group (n = 20), the IM group (n = 20), and the healthy control group (n = 20). Age distribution analysis indicated a non-normal distribution in the IM group, while the EDE and control groups showed normally distributed age data. Statistical analysis revealed a significant difference in age among the groups ($P < 0.05$). Age was expressed as median (P25, P75), with values as follows: EDE group: 55 (48.25, 65.75) years; IM group: 4 (3.00, 6.00) years; Control group: 33 (26.50, 44.50) years.

2.2 Sample Collection and Storage

Peripheral venous blood (5 mL) was collected from patients with EDE, IM, and healthy volunteers who met the inclusion criteria. Blood samples were placed into heparinized anticoagulant tubes and centrifuged at 3500 rpm for 10 minutes. The resulting plasma supernatants were collected, aliquoted into sterile, RNase/DNase-free 1.5 mL EP tubes, and labeled according to group and collection sequence: Drug eruption 1–20, IM 1–20, Control 1–20. All samples were stored at –80 °C until further analysis.

2.3 Reagents

ELISA kits for humanIL-5 and sFas-L were purchased from ABclonal Technology Co., Ltd. (Wuhan, China). Plasma cytokine concentrations were measured using enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocols.

2.4 Statistical Analysis

All statistical analyses were performed using SPSS version 25.0. Categorical data were analyzed using the chi-square test (χ^2 test). For continuous variables across the three groups, one-way ANOVA was applied to normally distributed data, while Kruskal–Wallis H test was used for non-normally distributed data. Results were presented as median (P25, P75). A P-value < 0.05 was considered statistically significant. Pairwise comparisons among the three groups were performed, and adjusted $P<0.05$ were considered indicative of significant intergroup differences. Binary logistic regression analysis was conducted using MedCalc to evaluate the combined predictive value of multiple cytokines.

3. Results

3.1 Plasma IL-5 Expression Levels and Differences among Eruptive Drug Eruption, IM, and Control Groups

The data from the eruptive drug eruption group were independent samples with a non-normal distribution, while the data from the IM group and the control group were independent and normally distributed. A rank-sum test was conducted to analyze the differences in IL-5 concentrations among the three groups. The findings demonstrated a statistically significant difference in the overall IL-5 distribution ($Z = 17.509$, $P < 0.05$). Plasma IL-5 levels were significantly elevated in both the IM group and the eruptive drug eruption group compared with the healthy control group ($P < 0.05$). However, no statistically significant difference was observed between the eruptive drug eruption group and the IM group ($P > 0.05$), as shown in Figure 1.

3.2 Plasma sFas-L Expression Levels and Differences among Eruptive Drug Eruption, IM, and Control Groups

The plasma sFas-L concentration data in the eruptive drug eruption group were independent samples with a non-normal distribution, whereas the data from the IM and control groups followed a normal distribution and were mutually independent. A rank-sum test was employed to analyze differences in sFas-L concentrations across the three groups. The results indicated a statistically significant difference in the

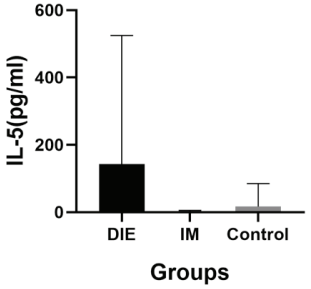

Fig 1. Plasma IL-5 expression levels among eruptive drug eruption, IM, and control groups

overall distribution of sFas-L levels ($Z = 15.736$, $P < 0.05$), as shown in Figure 2. Plasma sFas-L concentrations were significantly elevated in both the IM group and the eruptive drug eruption group compared to the control group (adjusted $P < 0.05$). However, no statistically significant difference in sFas-L levels was observed between the eruptive drug eruption and IM groups ($P > 0.05$), as shown in Figure 2.

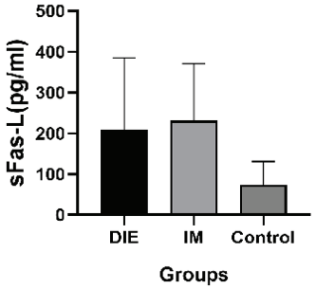

Fig 2. Plasma sFas-L expression levels among eruptive drug eruption, IM, and control groups

3.3 Differences in Clinical Parameters between Patients with Eruptive Drug Eruption and IM

Compared to the eruptive drug eruption group, patients in the IM group exhibited significantly higher rates of peripheral blood lymphocytosis, elevated creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH) levels, as well as a higher incidence of decreased serum phosphorus (P) levels ($P < 0.05$). Conversely, the rate of lymphocyte reduction in peripheral blood was significantly greater in the EDE group than in the IM group ($P < 0.05$).

4. Discussion

EDE is the most common manifestation of adverse drug reactions. A retrospective study reported that from 2003 to 2019, the annual hospitalization rate of patients with drug eruptions accounted for 9.45% to 10.01% of all dermatology inpatients. Various studies have shown that EDE comprise 45.8% to 95% of all drug eruptions[9, 10]. More than 50% of cases resolve spontaneously within two weeks after drug discontinuation. However, continued administration of the sensitizing drug may result in severe cutaneous adverse reactions (SCARs), such as exfoliative dermatitis or Stevens–Johnson syndrome (SJS), which may be life-threatening[4, 5].

IM is caused by infection with the Epstein–Barr virus (EBV), a member of the gammaherpesvirus subfamily. The disease primarily affects individuals in two age groups: 1–6 years and 14–20 years. Serological evidence shows that more than 90% of adults have experienced previous EBV infection. The virus is primarily transmitted through respiratory droplets, with blood-borne transmission being relatively rare. Key diagnostic tests include detection of anti-EBV capsid antigen IgM (EBV-CA-IgM) and IgG (EBV-CA-IgG) antibodies, quantitative EBV DNA testing, and morphological analysis of peripheral blood smears. A marked increase in atypical lymphocytes in peripheral blood, along with clinical features such as fever, pharyngeal erythema, lymphadenopathy, and hepatosplenomegaly, contributes to the diagnosis[11]. However, due to limited availability and longer turnaround times (up to one week) for EBV serological testing in some hospitals, timely diagnosis and treatment of IM can be delayed.

Both EDE and IM can manifest as similar cutaneous features, including erythema, papules, maculopapular rashes, petechiae, and urticaria. Moreover, the timing of rash onset in IM—occurring shortly after systemic symptoms—coincides with the sensitization period typically seen in EDE, and both conditions present challenges in laboratory-based differential diagnosis. Previous studies have investigated the differential expression of cytokines such as IL-2, IL-4, IL-5, IFN-γ, and sFasL in peripheral blood to distinguish between EDE and other viral exanthems such as measles, rubella, and parvovirus B19 infections. According to a study, IL-4 and IL-5 were elevated in patients with EDE, while IFN-γ levels remained unchanged. In contrast, IFN-γ levels were increased in patients with measles, rubella, and parvovirus infections, without concurrent elevation in IL-4 or IL-5[12]. The results showed a more prominent increase in IL-2 mRNA in the EDE group, while IL-4

mRNA was more elevated in the viral exanthem (VIE) group. IL-5 mRNA was undetectable in both groups. IFN-γ mRNA was elevated in both, but the difference was not statistically significant[13]. In another study, Stur used ELISA to evaluate serum sFasL levels in 42 patients with EDE and viral exanthems. Elevated sFasL levels were observed in EDE patients, particularly in those whose eruptions were induced by β-lactam antibiotics, allopurinol, anticonvulsants, or quinolones, whereas patients treated with lincosamides showed no such elevation. Neither viral exanthem patients nor healthy controls demonstrated increased sFasL levels. Notably, two patients with IM who had received ampicillin and subsequently developed exanthematous rashes showed markedly elevated serum sFasL levels[14]. However, a study involving seven patients with EDE and ten with viral-induced exanthems, found no significant difference in median serum sFasL levels between the two groups using ELISA [15, 16]. These findings suggest that while cytokine profiling holds potential for differential diagnosis, its utility in distinguishing EDE from viral exanthems—particularly IM-remains controversial and requires further investigation. Importantly, to date, few studies have specifically compared cytokine profiles in EDE and IM, which makes this study highly relevant. In the present study, ELISA was used to quantify plasma levels ofIL-5 and sFasL in patients with EDE and IM. The aim was to explore whether these immunological markers could assist in distinguishing the two clinically similar conditions.

The diagnostic significance of IL-5 in differentiating EDE from IM is also inconclusive. HARI et al. found that IL-5 was markedly elevated in patients with EDE[12], whereas Nakai reported no detectable increase in plasma IL-5 levels among IM patients[17]. Similarly, TORRES et al. found no detectable IL-5 mRNA expression in either drug-induced or virus-induced exanthematous cases[13]. Deschamps, using Luminex assay panels, also found no increase in IL-5 levels in either EDE or viral exanthem (including IM) patients[16]. In our study, plasma IL-5 concentrations were higher in EDE patients than in IM patients and healthy controls; however, the differences were not statistically significant in either comparison. These findings suggest that IL-5 may not serve as a reliable biomarker for differentiating EDE from IM in cases of overlapping rash morphology.

Several studies have explored the use of sFasL as a biomarker to differentiate between drug-induced exanthema (EDE) and viral exanthems, including IM (IM), but findings have been inconsistent. Some research suggests that sFasL is elevated in drug eruptions but not in IM [14], while other studies report a moderate elevation of sFasL in IM patients [18, 19]. Torres found no statistically significant difference in sFasL levels between patients with EDE and those with IM [13]. Moreover, Wang reported that FasL expression in lesional tissues was higher in EDE than in viral exanthems, including those caused by EBV [20].

In the present study, both EDE and IM patients exhibited significantly elevated peripheral plasma sFasL levels compared to healthy controls, with statistically significant differences. However, there was no statistically significant difference in sFasL levels between the EDE and IM groups themselves. These findings are consistent with those of TORRES et al., suggesting that plasma sFasL concentration is not a reliable marker for differentiating between EDE and IM in patients presenting with similar rash morphologies.

5. Conclusion

IL-5 levels were found to be elevated in both EDE and IM groups, but sFasL levels were limited value for differential diagnosis in patients presenting with erythematous and maculopapular rashes. Additionally, increased levels of peripheral lymphocytes, CK-MB, LDH, and decreased serum phosphorus are suggestive of IM, while lymphopenia is more indicative of drug eruption.

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