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Serum Level of Granulocyte-macrophage Colony-stimulating Factor in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Abstract

BACKGROUND: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions. Activated T-cells secrete high amounts of cytokines that increase the expression and activity of keratinocytes, including granulocyte-macrophage colony-stimulating factor (GM-CSF).

AIMS: The aims of this study were to evaluate the serum level of GM-CSF in SJS and TEN as well as the relationship between it and the progress of SJS and TEN.

METHODS: This was a sectional descriptive study conducted at the National Hospital of Dermatology and Venereology, in Hanoi, Vietnam, from October 2017 to September 2019. Forty-eight SJS/TEN patients, 43 erythema multiforme (EM) patients, and 20 healthy controls (HCs) participated. GM-CSF levels were measured using the fluorescence covalent microbead immunosorbent assay (ProcartaPlex Immunoassay Panels kit, Thermo Fisher Scientific, USA). The Mann–Whitney U-test was used to compare serum SJS/TEN levels of the two groups. The Wilcoxon tests were used to compare quantitative variables before and after the treatment. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS: There were 19 SJS patients (39.5%) and 29 TEN patients (60.5%). The mean age was 49.3 years, range of 19–77 years. The male patients were 47.9%. The most common causative drugs were traditional medicine (29.1%), followed by carbamazepine (12.5%), and allopurinol (12.5%). On the day of hospitalization, the mean serum level of GM-CSF in the SJS/TEN group was 10.6 pg/mL, which was significantly higher than that of the EM group ($p < 0.05$) but not higher than that of the HCs group and was higher than that on the day of re-epithelialization (3.6 pg/mL) and the difference was statistically significant with $p < 0.05$.

CONCLUSION: Serum GM-CSF level can be a good biomarker to evaluate the progress of SJS/TEN.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the most life-threatening of cutaneous adverse drug reactions (SCARs) [1]. The frequency of the disease in the population is only about 2/1,000,000 people, but the mortality rate may be up to 30% [2], [3], [4], [5]. The most common offending medicines causing SJS/TEN are allopurinol, carbamazepine, cotrimoxazole, abacavir [6], [7], and even traditional medicine. In SJS/TEN, the first symptoms may be fever, and respiratory inflammation, then, there are mucous membrane lesions on the eyes, mouth, and genital regions. The skin becomes necrotic, and detachment, forming blisters. Patients with SJS/TEN can be mortal due to bacterial infection or failure of internal organs. Neutropenia is also observed in patients with SJS/TEN [8].

The main pathophysiological feature of SJS/TEN is extensive necrosis and apoptosis of keratinocytes [9], a process initiated by drug-induced cytotoxic T lymphocytes [10], [11]. Drug presentation limited by major histocompatibility complex or human leukocyte antigen class I leads to the proliferation of TCD8+ [7], which infiltrates skin, and produces soluble factors that make apoptosis of keratinocytes [9], [12].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is an important hematopoietic growth factor and immune modulator. GM-CSF also has profound effects on the functional activities of various circulating leukocytes. It is produced by a variety of cell types including T-cells, macrophages, endothelial cells, and fibroblasts on receiving immune stimuli [13]. Tear cytokine profiling of chronic SJS cases revealed significant upregulation of GM-CSF, interleukin (IL)-8, IL-1β, monocyte chemoattractant protein-1, IL-15, IL-2, and IL-17A [14].

In the early phase, SJS/TEN may have skin manifestations similar to erythema multiforme (EM) [1], [15], [16], but no rapid test can distinguish them clinically. Histologically, there is more infiltration of inflammatory cells in EM than in SJS/TEN [5]. We performed this study to measure the serum level of

GM-CSF in the SJS/TEN group, compare it with that in the EM group and the healthy controls (HCs) group, and evaluate the relation between it and the progress of SJS/TEN.

Methods

Study design and ethical clearance

This was a sectional descriptive study that had been approved by the Ethical Review Committee on Research Involving Human Subjects, Hanoi Medical University (Number 04NCS17, dated February 8, 2018). Written consent was obtained from all participants. It was conducted at the National Hospital of Dermatology and Venereology, in Hanoi, Vietnam, from October 2017 to September 2019.

Patients

In total, 48 patients with SJS/TEN were enrolled. The SJS/TEN patients had their vital signs, systemic symptoms, and the percentage of body surface area affected (skin detachment) examined. Some routine blood and urine tests were conducted. SJS and TEN were classified by Bastuji-Garin, based on the percentage of epidermal detachment area: (i) SJS: <10%, (ii) TEN: >30%, and (iii) overlapping SJS/TEN: 10%–30% [1]. Inclusion criteria were age more than 17 years old, and admission <10 days after onset (that was defined as the day mucocutaneous or ocular lesions were first eroded or ulcerated) of SJS/TEN. Exclusion criteria were human immunodeficiency virus positivity and cases of multi-organ failure and sepsis. In addition, 43 EM patients and 20 HCs participated in this study as comparison groups. The SJS/TEN and EM patients were treated with systemic corticosteroids at the dose of 1–2 mg prednisolone/kg/day in combination with care support.

Analysis cytokines

For 48 SJS/TEN patients, we took blood samples at two-time points: (1) On the day of hospitalization, and (2) on the day of re-epithelialization. For EM patients and HCs, the blood was taken at one point, before the treatment. All blood samples were left to coagulate at room temperature for 10–20 min, then centrifuged for 20 min at a speed of 2000–3000 r.p.m, and, finally, serum was taken and stored at −80°C until proceeding with the cytokine measurement. We measured serum GM-CSF levels using the fluorescence covalent microbead immunosorbent assay (ProcartaPlex Immunoassay Panels kit, Thermo Fisher Scientific, USA).

Statistical analysis

Data entry and analysis were conducted using SPSS software version 16.0 (IBM, Armonk, NY, USA). The Mann–Whitney U-test was used to compare serum GM-CSF levels of the two groups. The Wilcoxon tests were used to compare quantitative variables before and after the treatment of the SJS/TEN group. Differences were considered to be statistically significant at $p < 0.05$.

Results

Nineteen SJS patients (39.5%) and 29 TEN patients (60.5%) participated in our study. Their characteristics are shown in Table 1. The mean age was 49.3 years, range of 19–77 years (47.9% males and 52.1% females). The most common causative drugs were traditional medicine (29.1%), carbamazepine (12.5%), and allopurinol (12.5%). The time between the onset and the day of hospitalization was 5.9 days (range 2–18 days). The mean body surface area affected was 43.7% of the total body surface area. The percentage of fever, mucous membrane lesions, neutropenia, and pneumonia were 56.2%, 81.2%, 13.3%, and 16.7%, respectively. The mean time of re-epithelialization was 15.9 days (range 9–31 days). All SJS/TEN patients got re-epithelialization and total resolution, and no one with in-hospital mortality.

Table 1: Demographic, clinical, and paraclinical characteristics of SJS/TEN patients

Characteristics	Results
Classification, n (%)	
SJS	19 (39.5)
TEN	29 (60.5)
Age (years)	49.3 ± 15.0
Sex, n (%)	
Male	23 (47.9)
Female	25 (52.1)
Causative drugs, n (%)	
Traditional medicine	14 (29.1)
Carbamazepine	6 (12.5)
Allopurinol	6 (12.5)
Antibiotics	3 (6.2)
NSAIDs	4 (8.4)
Thalidomide	1 (2.1)
Unknown	14 (29.2)
The time between onset and hospitalization (days)	5.9 ± 2.7
Body surface area affected (%)	43.7 ± 34.7
Fever, n (%)	27 (56.2)
Mucous membrane lesions	39 (81.2)
Pneumonia	8 (16.7)
Neutropenia, n (%)	11 (13.3)
High level of liver enzymes, n (%)	55 (66.3)
Kidney dysfunction, n (%)	33 (39.8)
The time of re-epithelialization (days)	15.9 ± 4.6

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, NSAIDs: Non-steroid anti-inflammatory drugs.

On the day of hospitalization, the mean serum GM-CSF level of the SJS/TEN group was 10.6 pg/mL, ranging from 3.1 pg/mL to 87.8 pg/mL. This level was significantly higher than that of the EM group ($p < 0.05$) but not higher than that of the HCs group. The mean serum GM-CSF level of the HCs group was significantly higher than that of the EM group ($p < 0.05$) (as shown in Table 2 and Figure 1).

Table 2: The serum levels of GM-CSF in SJS/TEN, erythema multiforme and healthy controls groups

Serum level of GM-CSF (pg/mL)	SJS/TEN (n = 48)	EM (n = 43)	HCs (n = 20)	p (Mann-Whitney U test)
Mean ± SD	10.6 ± 19.2	6.3 ± 14.6	10.4 ± 15.6	p1 < 0.05
Median	3.1	3.1	3.1	p2 > 0.05
Range	3.1–87.8	3.1–79	3.1–55.5	p3 < 0.05

p1: SJS/TEN versus EM, p2: SJS/TEN versus HCs, p3: EM versus HCs. SD: Standard deviation, GM-CSF: Granulocyte-macrophage colony-stimulating factor, EM: Erythema multiforme, HCs: Healthy controls, SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis.

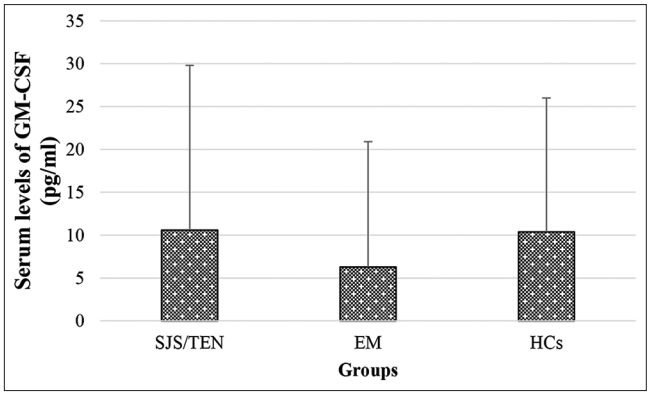

Figure 1: Serum levels of GM-CSF in SJS/TEN, EM, and HCs groups

The mean serum level of GM-CSF in the SJS/TEN patients with the onset of fewer than 6 days was 13.5 ± 24.9 pg/mL, not higher than that of patients with the onset of more than 6 days (7.3 ± 8.8 pg/mL), p > 0.05 (Mann–Whitney U-test), as shown in Table 3 and Figure 2.

Table 3: Serum levels of GM-CSF in the SJS/TEN group following the day of onset

Serum level of GM-CSF (pg/mL)	The day of onset		p (Mann-Whitney U test)
	< 6 days (n = 25)	≥ 6 days (n = 23)	
Mean ± SD	13.5 ± 24.9	7.3 ± 8.8	> 0.05
Median	3.1	3.1	
Range	3.1–87.7	3.1–30	

SD: Standard deviation, GM-CSF: Granulocyte-macrophage colony-stimulating factor.

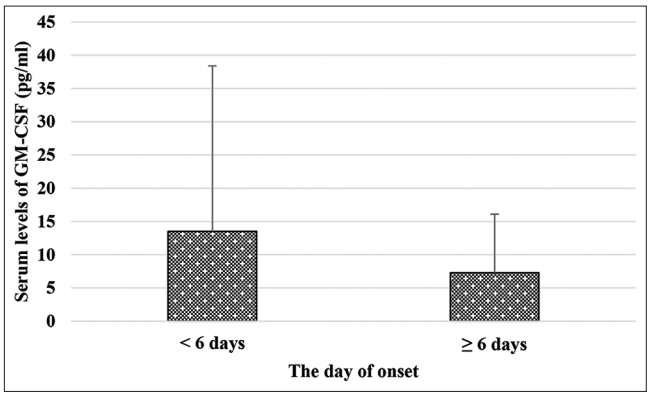

Figure 2: Serum levels of GM-CSF in the SJS/TEN group following the day of onset

The mean serum level of GM-CSF in the SJS/TEN patients using systemic corticosteroids before hospitalization was 10.6 pg/mL, lower than that of the SJS/TEN patients without using systemic corticosteroids (12.9 pg/mL), but the difference was not statistically significant with p > 0.05 (Mann-Whitney U test), as shown in Table 4 and Figure 3.

Table 4: Serum levels of GM-CSF in the Stevens-Johnson syndrome/toxic epidermal necrolysis group following the use of systemic corticosteroids before hospitalization

Serum level of GM-CSF (pg/mL)	The use of systemic corticosteroids before hospitalization		p (Mann-Whitney U test)
	Yes (n = 20)	No (n = 21)	
Mean ± SD	10.6 ± 22.1	12.9 ± 19.6	> 0.05
Median	3.1	3.1	
Range	3.1–83.4	3.1–87.7	

SD: Standard deviation, GM-CSF: Granulocyte-macrophage colony-stimulating factor.

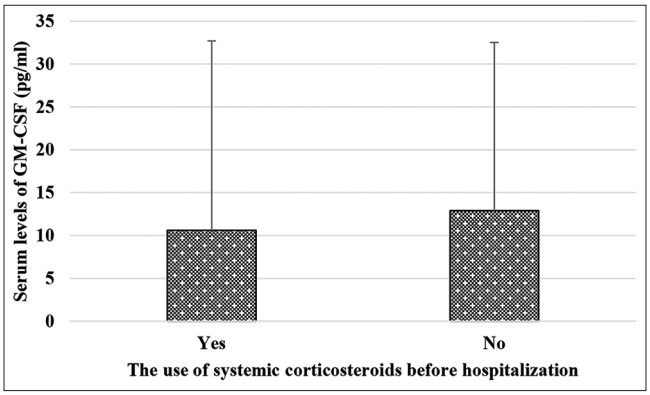

Figure 3: Serum levels of GM-CSF in the SJS/TEN group following the use of systemic corticosteroids before hospitalization

The mean serum level of GM-CSF in the SJS/TEN patients on the day of hospitalization was 10.6 pg/mL, higher than that on the day of re-epithelialization (3.6 pg/mL) and the difference was statistically significant with p < 0.05 (Wilcoxon test), as shown in Table 5 and Figure 4.

Table 5: Serum levels of GM-CSF in Stevens-Johnson syndrome/toxic epidermal necrolysis patients on the day of hospitalization and the day of re-epithelialization

Serum level of GM-CSF (pg/mL)	The day of hospitalization (n = 48)	The day of re-epithelialization (n = 48)	p (Wilcoxon test)
Mean ± SD	10.6 ± 19.2	3.6 ± 3.7	< 0.05
Median	3.1	3.1	
Range	3.1–87.7	3.1–29.9	

SD: Standard deviation, GM-CSF: Granulocyte-macrophage colony-stimulating factor.

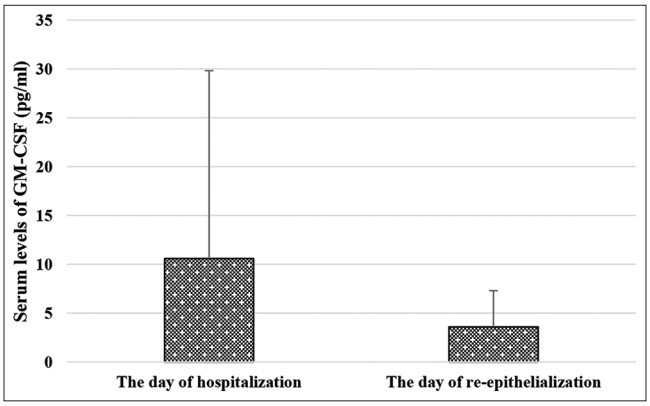

Figure 4: Serum levels of GM-CSF in the SJS/TEN group on the day of hospitalization and the day of re-epithelialization

Discussion

In our study, the serum GM-CSF concentration in the SJS/TEN group was higher

than that in the EM group ($p < 0.05$), but similar to the HCs group, it was unaffected by prehospital corticosteroid use. After re-epithelialization, the serum concentration of GM-CSF decreased to 3.6 pg/mL, the change was statistically significant with $p < 0.05$. The immunomodulatory and regenerative role of granulocyte-colony-stimulating factor (G-CSF) is used in the treatment of SJS/TEN. This therapy helps to stop hypersensitivity, stimulate epidermal regeneration, and control neutropenia [8], [17], [18]. Recent intensive investigations are centered on the application of GM-CSF as an immune adjuvant for its ability to increase dendritic cell maturation and function as well as macrophage activity. It is used clinically to treat neutropenia in cancer patients undergoing chemotherapy, AIDS patients during therapy, and patients after bone marrow transplantation. Interestingly, anti-GM-CSF was found to be more effective than anti-tumor necrotic factor-alpha (TNF-α) in treating rheumatoid arthritis [13], [19].

After its identification, GM-CSF was considered to be a proinflammatory cytokine [19]. It may play an essential role in various human inflammatory diseases, for example, rheumatoid arthritis, inflammatory renal disease, and inflammatory lung disorders. In a collagen-induced arthritis model, it has been reported that GM-CSF−/−mice develop no disease, and the humoral response to collagen was uncompromised [13], [20]. It is in line with the fact that, in SJS/TEN, there is an increased serum level of some cytokines and chemokines, for example, TNF-α and interferon-gamma (IFN-γ).

GM-CSF can both increase antigen-induced immune responses and alter the T helper type 1 (Th1)/T helper type 2 (Th2) cytokine balance. It has recently been shown that mice lacking GM-CSF die rapidly from severe necrosis when exposed to an aerosol-delivered infection of *Mycobacterium tuberculosis* due to their inability to mount a Th1 response [13], [21]. GM-CSF over-expression, however, failed to focus T-cells and macrophages into sites of infection, suggesting that uncontrolled expression of GM-CSF leads to defects in cytokine and chemokine regulation. Therefore, excess GM-CSF does not induce an overly Th1 response and very fine control of GM-CSF is needed to fight infections [13]. Caproni *et al.* showed that skin biopsies of SJS/TEN expressed all cytokines (TNF-α, IFN-γ, IL-2, IL-5, IL-13, CCR3 [C-C chemokine receptor type 3], CXCR3 [C-X-C motif chemokine receptor 3], and CXCR4) were stronger than EM skin samples. SJS/TEN and EM skin samples expressed more potent cytokines than healthy human skin samples. A comparison of Th1 or Th2-related cytokines showed that the Th1 response was dominant in EM, and the imbalance between Th1 and Th2 was not significant in SJS/TEN [22].

Activated T-cells are one of the major sources of GM-CSF; however, the specific phenotype of T-cells producing GM-CSF has not been identified. T-cells seem to lose their ability to synthesize GM-CSF during differentiation. Both Th1 and Th2 cytokines, such as IFN-γ, IL-12, IL-4, and IL-10, negatively regulate GM-CSF production, but the function of GM-CSF is not well delineated in activated or differentiated helper T-cells [13]. In this study, the serum level of GM-CSF in the SJS/TEN groups was not higher than that in the HCs group. It may be due to that in SJS/TEN, cytokines of Th1 (TNF-α and IFN-γ) were produced more than normal.

Alpha-beta T-cell receptor+, CD4, and CD8+ T-cells are involved in different drug eruptions, their function outlines the clinical picture. In maculopapular, bullous, and pustular exanthematous eruptions, cytotoxic T-cells play an important role, while a high IL-5 is frequently found in maculopapular and occasionally in bullous and pustular exanthems. High IL-8 (CXCL-8) and GM-CSF production by T-cells is a hallmark of pustular drug exanthems. This can explain why in this study, serum levels of GM-CSF were not high in SJS/TEN patients. In most SCARs (SJS/TEN, drug reaction with eosinophilia and systemic symptoms, fixed drug eruptions), cytotoxic CD8+ T-cells with natural killer cell markers can be found in the blister fluid [23]. They can produce toxic proteins such that granulysin, granzyme B, and perforin which play an important role in the apoptosis of keratinocytes [7], [9].

These findings are the basis for a new subclassification of delayed, type IV hypersensitivity reactions into type IVa (Th1 cells, e.g., tuberculin reaction and contact dermatitis), IVb (Th2 cells, maculopapular exanthem with eosinophilia), IVc (cytotoxic T-cells, contact dermatitis, maculopapular, and bullous exanthem), and IVd reactions (CXCL-8/GM-CSF-producing T-cells and neutrophil attraction, pustular exanthems), by which, in most reactions, various mechanisms cooperate but one reaction determines the clinical picture [23].

This study has some limitations, for example, serum samples of SJS/TEN and EM groups were taken conveniently on the day of hospitalization, and some patients were already treated with systemic corticosteroids. In addition, other inflammations those patients suffered from at the same time could affect the production of GM-CSF.

Conclusion

In SJS/TEN patients, serum GM-CSF level is higher than those in EM patients; after re-epithelialization, it decreases significantly compared to that before treatment. Serum GM-CSF

can be a good biomarker to evaluate the progress of SJS/TEN.

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