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Cytokine Background of Peripheral Blood - A Predictor of the Development of Herpes-Associated Erythema Multiforme Exudative

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Abstract Background: Herpes-associated erythema multiforme exudative is a recurrent inflammatory disease of the skin and mucous membranes that develops predominantly in response to herpes simplex virus reactivation. The severity and recurrence of the disease are closely linked to the nature of the immune response, particularly the cytokine balance between T-helper type 1 and type 2 cells. However, data on cytokine-based prognostic markers remain scarce. Objective: To identify the peripheral blood cytokine profile in patients with herpes-associated erythema multiforme exudative and generalized recurrent herpes during relapse, and to assess their prognostic significance for mucocutaneous involvement. Methods: The study included 132 participants: 75 with herpes-associated erythema multiforme, 22 with generalized recurrent herpes infection, and 35 healthy controls. Serum levels of interferon-gamma, tumor necrosis factor-alpha, interleukin-4, and interleukin-10 were measured using enzyme-linked immunosorbent assay. Statistical analysis was performed using the Student's t-test or Mann–Whitney test ($p < 0.05$). Results: During relapse, patients with herpes-associated erythema multiforme had significantly increased levels of interleukin-4 (64.65 ± 1.84 pg/ml) and interleukin-10 (78.11 ± 2.13 pg/ml), and markedly decreased levels of interferon-gamma (0.43 ± 0.14 pg/ml) and tumor necrosis factor-alpha (0.15 ± 0.06 pg/ml), compared to controls. These deviations persisted to a lesser extent during remission. Cytokine patterns in generalized recurrent herpes were less pronounced. Conclusions: A Th2-dominant cytokine profile characterizes herpes-associated erythema multiforme and may predict disease relapse. Cytokine monitoring could improve early diagnosis and guide personalized immunotherapy.

Keywords Herpes-associated erythema multiforme, Cytokine profile, IFN-γ, TNF-α, IL-4, IL-10, Th1/Th2 balance, Herpes simplex virus, Relapse, Immunological predictor

1. Introduction

Herpes-associated erythema multiforme exudative (HAEM) is an inflammatory disease of the skin and mucous membranes that occurs mainly against the background of reactivation of the herpes simplex virus (HSV). The disease often has a recurrent course and can significantly reduce the quality of life of patients [1,3,6,14]. The trigger is the viral load, but clinical manifestations are determined by the nature and severity of the immune response. Of particular interest is the cytokine background as a reflection of the pathogenetic processes underlying the exacerbation and chronicity of the disease [2,5,7,15].

It was found that GRP (generalized recurrent herpes), preceding the development of HA MEE, is characterized by a staged course with alternating phases of remission and relapse. Immunological analysis showed that in the early stages of inflammation, cytokines of the Th2 response dominate, while the late phase and remission are associated with the activation of Th1 cells. This switch in the immune response is accompanied by a change in the production of cytokines and can be reflected in an increase in the IgG level, which, in turn, is associated with the transition to the manifest form of MEE [3,4,8,16].

In this context, the cytokine profile of peripheral blood is considered not only as a reflection of the stage of inflammation, but also as a potential predictor of the transition of herpesvirus infection to a cutaneous form with epithelial damage. Proinflammatory cytokines (IFN-γ, TNF-α) and anti-inflammatory (IL-4, IL-10) play a key role in the balance between tolerance and aggression of the immune response, forming an individual risk of developing HA MEE [6,8,13,18].

To date, systemic data on immune predictors of the development of HA EME are limited, which complicates targeted prevention and early immunomodulatory therapy. Studying the cytokine background in the peripheral blood of

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patients with GERD and HA EME will help clarify the pathogenetic mechanisms of the transition of latent herpes infection to an inflammatory skin process [3,7,11,17].

Thus, the study of the cytokine profile in patients with herpes infection acquires practical significance both for the prognosis of relapses and for the development of personalized treatment regimens and prevention of HA EME. This topic is relevant from the point of view of clinical immunology, dermatology and translational medicine.

Purpose of the study: To identify the features of the cytokine profile of peripheral blood in patients with herpes-associated erythema multiforme exudative (HAEME) and generalized recurrent herpes infection (GRH) in the relapse phase in order to assess their prognostic significance in the formation of cutaneous and mucosal manifestations of the disease.

2. Material and Methods

The study included 132 patients stratified into three groups: the main group consisted of 75 patients with herpes -associated erythema multiforme exudative (HAEM) in the relapse phase; the comparative group included 22 patients with generalized recurrent herpes infection (HRI) without mucocutaneous manifestations; the control group consisted of 35 practically healthy volunteers. All participants underwent determination of the levels of key proinflammatory and anti-inflammatory cytokines in the blood serum: interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin-4 (IL-4) and interleukin-10 (IL-10). The study was performed by enzyme-linked immunosorbent assay (ELISA) using certified commercial kits in accordance with the manufacturer's instructions. The measurement results are expressed in pg/ml. Statistical processing of the obtained data was performed using the Statistica 10.0 software package. To assess differences between groups, Student's t-test (for normal distribution) and Mann-Whitney test (if not available) were used. Differences were considered statistically significant at $p<0.05$.

3. Results and Disscusion

The above serves as the basis for determining the nature of disturbances in the state of the cytokine network of peripheral blood in patients with GA MEE during relapse and remission in comparison with the group of patients with GR.

The results of the study of the cytokine profile of peripheral blood of patients with HA EME are presented in Fig. 1.

During a relapseIn patients with HA EME (Fig. 1), there is a significant increase in the concentration of cytokines produced by Th type 2 (IL-4, IL-10) - 64.65 ± 1.84 pg / ml and 78.11 ± 2.13 pg / ml, respectively, compared to the control group, where the amount of IL-4 was 18.11 ± 1.64 pg / ml, and IL-10 - 56.11 ± 2.86 pg / ml. Moreover, these indicators are also higher than those in patients with GRP - 51.28 ± 0.8 pg / ml and 71.11 ± 1.78 pg / ml, ($p<0.05$).

In case of relapse of HA EME, a decrease in the produced Th type 1 cytokines - IFN-γ, TNF-α - was revealed. Thus, if the content of IFN-γ in the peripheral blood in the control was 2.39±0.73 pg/ml, then in case of relapse of HA EME - 0.43±0.14 pg/ml, and this is significantly less than in patients with relapse of GRP (0.59±0.26 pg/ml), ($p<0.05$). A similar trend with TNF-α - 0.15±0.06 pg/ml in case of relapse of GA MEE, compared to the control - 1,19±0.13 pg/ml and GRP in relapse - 0.27±0.17 pg/ml, ($p<0.05$).

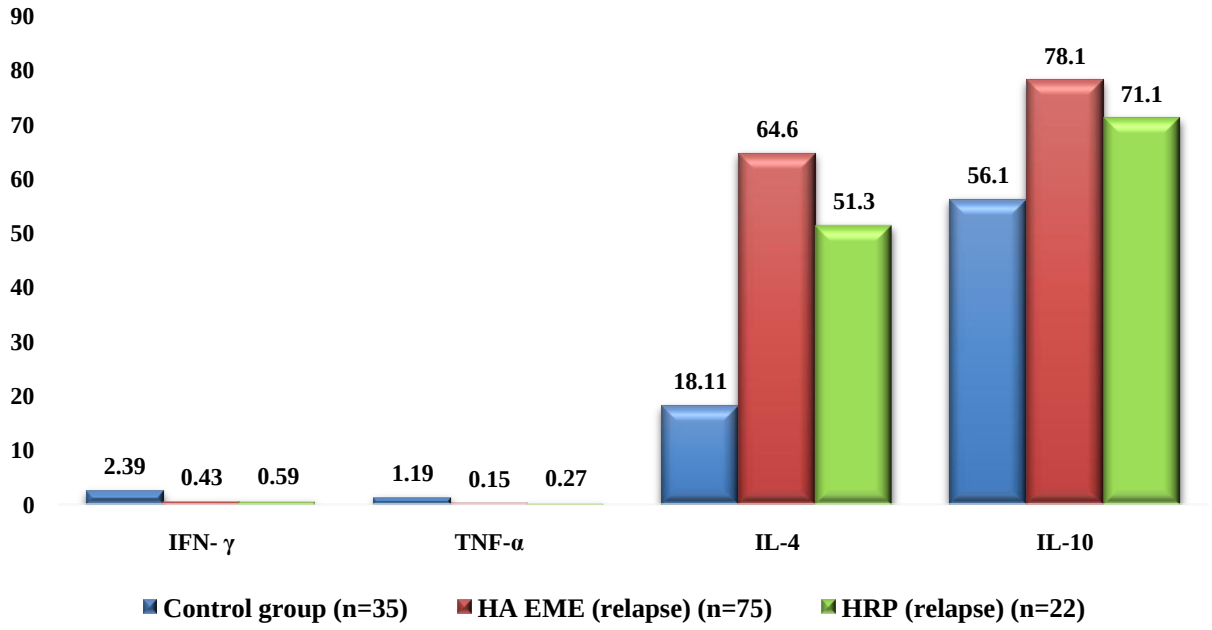

Figure 1. Th1 and Th2 cytokine profile indices in serum of patients with HA EME during relapse pg/ml

In most patients of group I, with manifestations of HA EME, an increase in the concentration of specific IgG in the peripheral blood was observed not only during relapse, but also during remission. Thus, taking into account the key role of some cytokines in the mechanism of IgG production, their difference was determined during the period of relapse and remission of the disease. The results of studies of the level of serum cytokines in patients with HA EME during remission of the disease are presented in Table 1.

Table 1. Th1 and Th2 cytokine profile indicators in patients with HA EME during remission

Cytokines, pg/ml	Control group (n=35)	HA EME (remission) (n=75)	GRP (remission) (n=25)	R
IFN-γ	2.39±0.73	1.5±0.1	1.82±0.2	<0.05
TNF-α	1.19±0.13	0.67±0.04	0.65±0.17	<0.05
IL-4	18.11±1.64	32.32±1.18	25.0±0.35	<0.05
IL-10	56.11±2.86	68.11±2.23	55.02±0.22	<0.05

Note: Significance when compared with the control group, ($p<0.05$)

The dynamics of the Th1 and Th2 cytokine profile indicators during the remission period was reliably manifested in relation to both patients with HA EME and GRP, although it could be said that the severity of deviations of these indicators from the control in HA EME is more significant. The level of cytokines produced by the Th1 type - IFN-γ, TNF-α, with a control indicator of 2.39±0.73 pg/ml and 1.19±0.13 pg/ml, respectively, was 1.5±0.1 pg/ml and 0.67±0.04 pg/ml in HA EME and were lower than those in remission of GRP - 1.82±0.2 pg/ml and 0.65±0.17 pg/ml, respectively, ($p < 0.05$). The level of increase in cytokines produced by Th2 type (IL-4, IL-10) was lower than similar indicators in relapse of both HA EME and GRP. During remission, IL-4 in patients with HA EME dropped to 32.32±1.18 pg/ml, but was 1.78 times higher than in the control, GRP - the ratio to the control was 1.38 times (25.0±0.35 pg/ml). The level of IL-10 cytokine practically normalized in patients with GRP during remission, and in patients with HA EME it remained significantly elevated - 68.11±2.23 pg/ml (1.21 times).

Our results allow us to state that a decrease in the synthesis of Th1 type cytokines during remission of HA EME may indicate an approaching relapse of the disease.

Th1 lymphocytes produce IFN-γ and TNF-α, activate macrophages, and Th2 lymphocytes produce IL-4 and IL-10, which signal B lymphocytes to begin IgG synthesis. Cytokines produced by Th2 lymphocytes stimulate the proliferation and differentiation of B lymphocytes and inhibit the activity of Th1 cells.

The present study shows that such a model of Th1/Th2 balance with a shift of the immune response towards the Th2 type largely explains the mechanisms of immunological processes in HA erythema. Patients with HA EME exhibit a pronounced biphasic type of Th-dependent immune response. In this case, the dominant Th2-dependent immune response manifests itself in a relapse of the disease, and Th1 - in remission. Taking these values into account, it is possible to more correctly influence the state of the immune system, and accordingly, the treatment of patients with HA EME.

4. Conclusions

- During the relapse of HA EME, there is an increase in the concentration of cytokines IL-4 by 3.57 times and IL-10 by 1.39 times and a decrease in the level of IFN-γ by 5.56 times, TNF-α by 7.93 times in the blood serum of patients compared to the control group;
- During remission of the disease, a reliable decrease in the concentration of IFN-γ by 1.59 times, TNF-α by 1.77 times in comparison with the control group and an increase in the level of IL-4 by 1.78 times and IL-10 by 1.21 times is observed;
- A clear difference in the cytokine profile of patients with HA EME from patients with GRP was revealed, which may indicate the role of cytokines in the formation of HA EME.

Study Limitations

No significant limitations were identified in the present study. All procedures were conducted under standard conditions, and the study sample was representative of the target population. However, further research with larger and more diverse samples is recommended to validate and expand upon these findings.

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Conflicts of Interest

The authors declare no conflicts of interest.

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