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Cytokines Induced Skin Adverse Reactions

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Abstract

Cutaneous adverse reaction is a common complication in association with the administration of cytokine products. Local inflammation reactions at the injection sites, widespread eruptions, exacerbation the primary autoimmune disorders and flu-like symptoms are frequently reported, besides, various rare side effects also have been observed. Though the exact mechanism is not clearly understood, the biological activities of cytokines in immunological reactions and impurities in biological products have been discussed.

Keywords: Adverse effect; Cytokine; Skin

Introduction

Cytokines are referred to polypeptides or small proteins with biological activities that are secreted by various cells. They are normal mediators of inflammation. In many instances, the interaction among different immunocytes is directly or indirectly mediated by cytokines, which play an extensive and complex role in immunological reactions. With the development of molecular medicine, cytokine products have been successfully used in clinical medicine. Postmarketing products (contain purified natural cytokines or recombinant products), such as interferon (IFN), granulocytecolony-stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoiesis stimulating factor (EPO), interleukin(IL)-1, IL-2, IL-3, IL-6, and tumor necrosis factor-α (TNF-α) have been used in a wide range of diseases. However, a variety of cutaneous reactions is observed in association with these agents.

Interferons

Interferon (IFN), a family of secretory glycoproteins, is an immune modulating agent that is used in the treatment of viral infections, tumors, and inflammatory conditions including multiple sclerosis [1]. The three main types of IFNs are classified according to their nucleic acid sequence: alpha, beta, and gamma. A wide range of diseases with recombinant IFNs and/or natural IFNs have been observed, and about 5-12% of side effects related to IFN treatment involve adverse skin reactions, either localized at the injection site or generalized skin reactions [2].

Interferon-α

IFN-α (subtypes: 2a, 2b, pegylated or not), mainly is used in the treatment of hepatitis C and B, AIDS, leukemia, or malignant tumor. Cutaneous reactions reported in the literature include localized reactions and generalized effects. Localized manifestations include redness, pain, swelling, induration, necrosis, granulomatous and suppurative dermatitis, lupus erythematosus-like pattern at inject site [3-5]. IFN-α occasionally be reported to induce facial erythema [6], aggravate autoimmune disorders such as lichen planus, psoriasis, SLE, eosinophilic fasciitis, sarcoidosis [6,7]. Although alopecia did not be reported separately, it appears to be the most common generalized cutaneous reaction reported, followed by transient and mild generalized rash-like reactions [8]. A review of the literature suggests that dermatological adverse reactions induced by pegylated IFN-a plus ribaverin (RBV) are various and frequent. Generalized eczema, hyperpigmented skin and tongue lesionsmultiple fixed drug eruption, vitiligopruritis, eruption, erythema, and hair shedding, eczema-like skin lesions, photosensitivity, vesicle erythematous eruptions, pruritic papular erythematous eruptionssecondary to combined treatment with peginterferon alfa-2a and ribavirin had been reported [9-17]. Tavakoli-Tabasi and Bagree [18] made a longitudinal cohort study, and suggested mucocutaneous reactions during IFN and ribavirin treatment of hepatitis C are associated with HIV infection and use of pegylated IFN. In their study, the most common dermatologic reactions were eczematous skin reactions, which occurred in 30 patients (10.5%). Distribution of the eczematous lesions predominantly located on the extensor surfaces of the extremities and on truncal skin sites exposed to friction [19]. In a recent study, pruritis, eruption, erythema, and hair shedding at injection sites occurred in 1/4 of the patients [15]. In another study, secondary hyperpigmentation occurs as an adverse event in 21% of patients, especially in those with dark skin types who have unprotected sun exposure so for these patients, sun protection should be advised. Uchida et al. suggested the monitoring of the plasma concentrations of ribavirin at Week 1 may provide an efficient tool for safe management of ribavirin therapy combined with IFN in order to predict the adverse reactions [20,21].

Interferon-β

IFN-β (subtypes: 1a, 1b), prescribed for multiple sclerosis (MS), are frequently associated with local injection-site reactions and a wide spectrum of generalized cutaneous adverse events. The most frequently reported being erythema, lipoatrophy and various immune-mediated disorders, such as psoriasis [22,23]. Besides, flu-like syndrome is observed in approx 60% of patients at the initiation of treatment [24]. Other rare cutaneous reactions include cutaneous necrosis, ulcers, granulomatous dermatitis, Raynaud's phenomenon, fixed drug eruption, lupus-like pattern, subacute cutaneous lupus erythematosus, and lupus panniculitis [5,25-31].

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Interferon-γ

IFN-γ was used as therapy for several diseases, including rheumatoid arthritis, psoriatic arthritis, psoriasis, chronic granulomatosis, and lepromatous leprosy infections. IFN-γ treatment has several adverse effects, including flu like symptoms, local redness, pain, and swelling, and was involved in the unexpected exacerbation of multiple sclerosis [32,33]. Erythema nodosum leprosum induced by prolonged treatment with recombinant IFN-γ in lepromatous leprosy patients had been observed [34]. Besides, IFN-γ appears to be a key pathogenic cytokine in psoriasis. It induced many molecular and histological features characteristic of psoriatic lesions, though there were no visible changes in the skin [35].

Granulocyte and Granulocyte-Macrophage Colony-Stimulating Factors (G-CSF and GM-CSF)

Granulocyte and granulocyte-macrophage colony-stimulating factors (G-CSF and GM-CSF) are growth factors that promote proliferation and maturation of bone marrow stem cells. Both of them have been investigated for the treatment of granulocytopenia result from autologous bone marrow transplantation and chemotherapy, AIDS, aplastic anemia, leukemia and so on. Several cutaneous eruptions have been reported in relation to these treatments. Locally induced eruptions, at injections sites, such as nodule or erythematous edematous plaque and neutrophilic dermatosis, like Sweet's syndrome, bullous pyoderma gangrenosum, cutaneous vasculitis have been reported [36-42]. Robak et al. reported a case of toxic epidermal necrolysis in a patient with severe aplastic anemia treated with cyclosporin A and G-CSF [43]. It seems that GM-CSF produced more frequent injection-site reactions and skin rash. Although it is not known how the administration of the recombinant human cytokine in pharmacologic doses results in the expression of a cutaneous eruption, there are some clues that it could induce changes in the immunologic status of the skin [44]. Patients should be monitored for development of inflammatory processes during G-CSF or GM-CSF therapy and this therapy should be given with caution to those patients with existing inflammatory conditions.

Erythropoietin (EPO)

EPO, mainly be used for the treatment of anemia, has limited cutaneous adverse consequences. Generalized eczema and exfoliative dermatitis associated with EPO have been reported [45-47].

Interleukin-1

IL-1 has antitumor activity and can be used for the therapy of malignant tumor or bone marrow depression caused by chemoradiation. Because it induces a capillary leak phenomenon and has other severe side effects, its use is limited. A eruption associated with chemotherapy after pretreatment with recombinant interleukin-1alpha has been reported [46].

Interleukin-2

IL-2 is a cytokine produced by human T lymphocytes and is involved in regulating immune reactions. Recombinant IL-2 is approved for the treatment of genital warts, sensitization dermatitis, malignant tumor, infection viral. Dermatologic changes associated with IL-2 administration are fairly common, such as injection site reaction, rash generalized edema, pruriginous erythema [48,49]. Cutaneous adverse effects are frequent, but generally mild and reversible, however, high-dose interleukin-2 (HD IL-2) treatment is associated with significant acute toxicities, mainly revolving around vascular leak syndrome, rarely, recurring cutaneous eruption [50]. Toxic epidermal necrolysis associated with interleukin-2 had been reported [51]. The 67-year-old kidney cancer patient died 10 days after treatment was begun. Similar to the case, in clinical practice, we encountered a severe IL-2 induced cutaneous adverse reaction, an immunocompromised patient performanced an acute scalded skin-like adverse reaction after IL-2 therapy. Blisters and bullas were found under the widespread erythema (Figure 1). This suggested that the use of IL-2 in immunocompromised patients must be given on an individualized basis.

Interleukin-3

Interleukin-3 is a hematopoietic growth factor derived from T lymphocytes. Recombinant human IL-3 (rhIL-3) is currently undergoing clinical trials in patients with marrow failure, aleukia, autologous bone marrow transplantation, immunoadjuvants [52-55]. The most frequent adverse effects of rhIL-3 are flu-like symptom, minor erythematous reactions at the injection sites, and urticaria [56].

Interleukin-6

IL-6 is a pleiotropic cytokine that plays a key role in the inflammatory processes by inducing the activation of several cells involved in immune response [57]. Recombinant human IL-6 (rhIL-6) has been used for immunodeficiency, malignant tumor, immunoadjuvants. Moderate injection-site reactions, cutaneous eruption consisting of coalescent, erythematous, scaling macules and papules after administration of recombinant human IL-6 had been reported [58,59].

Tumor Necrosis Factor-α (TNF-α)

TNF-α is produced by activated macrophages and monocytes. TNF-α, whose indications are malignant tumor, leukemia, bone marrow transplantation, cut down cholesterol, has few cutaneous adverse reactions include flulike symptom and local reactions [60,61].

Classification

Summarizing the current literatures in the field, we divide the adverse reactions into four categories (Table 1).

Erythematous dermatitis-like lesions

Erythema, eczematous reactions, eruptions, maculopapular erythema widespread or limited to injection sites can be observed in this group. They are similar to traditional exanthesis drug eruption

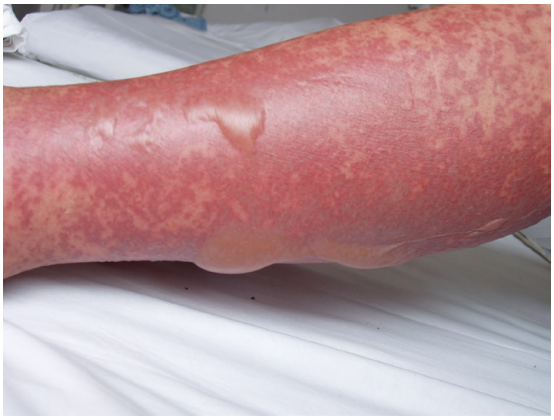

Figure 1: Acute scalded-like adverse reaction after undergoing treatment with IL-2. Blisters and bullas could be found under the widespread erythema. (From Li-Tao Zhang).

Cytokine	Indication	Skin adverse reactions
IFN-α	Leukemia, Kaposi's sarcoma, hepatoma, malignant tumor, AIDS, hepatitis C and B, Behcet disease, hemangiomas, keloids, actinic keratosis, cutaneous T-cell lymphoma, keloids, advanced melanoma	Local redness, pain, swelling, induration, necrosis or purulent actions at the injection sites, flu-like symptom, urticaria, pigmentation, multiple fixed drug eruption, erythema dermatitis, eczematous reaction, bullous lesions, cutaneous vasculitis, sarcoidosis-like lesion, alopecia areata, hair color change, lichen planus, lichenoid eruptions, granuloma, vitiligo, raynaud's phenomenon, xerostomia, livedo reticularis, seborrheic dermatitis, angioedema, aphthous ulcer, rehumatiod and lupus-like symptoms, induce or aggravate autoimmune disorders (such as psoriasis, eosinophilic fascitis, anasarca, paraneoplastic pemphigus, herpes labialis, and systemic lupus erythematosus) [4,6,8,10,11,16,32,69,75-79]
IFN-β	Multiple sclerosis	Local inflammatory reactions, nodule, necrosis and ulcers at the injection sites, flu-like symptom, subacute cutaneous lupus erythematous, severe urticaria, vasculitic-like lesion, sarcoidosis, allergic contact dermatitis, aggravate autoimmune disorders (such as psoriasis) [25,30,80-82]
IFN-γ	Chronic granuloma, genital warts, Rheumatoid arthritis, nsitization dermatitis, malignant tumor, infection viral, atopic dermatitis	Local redness, pain and swelling, erythema nodosum leprosum, flu-like symptoms, SLE-like symptom, aggravate the inflammation of eczema [32,34,83]
G-CSF	Granulocytopenia result from autologous bone marrow transplantation and chemotherapy, AIDS, aplastic anemia, leukemia	Nodule at the injection sites, exanthematic eruption, severe toxic epidermal necrolysis, leukocytoclastic vasculitis, pseudotumor hyperplasia, neutrophils sweat duct inflammation, Sweet's syndrome, bullous pyoderma gangrenosum, cutaneous vasculitis or follicultitis [36,41,43,72,84-88]
GM-CSF	Granulocytopenia result from autologous bone marrow transplantation and chemotherapy, AIDS, aplastic anemia, wound healing, cutaneous T-cell lymphoma, melanoma, chronic ulcers	Urticaria, edema, local or widespread erythematous dermatitis-like skin lesion, pustules or necrotizing vasculitis at the injection sites, aggravate the primary lesion, such as Sweet's syndrome, bullous pyoderma gangrenosum, psoriasis, psoriatic arthritis, cutaneous vasculitis [32,41,71,72,81]
EPO	Anemia induced by chronic renal failure, malignant tumor or chemotherapy	Generalized eczema, exfoliative dermatitis [45,46]
IL-1	Bone marrow depression caused by chemoradiation, malignant tumor	Flu-like symptom, erythematous dermatitis-like skin lesion, aggravate the primary lesion [47]
IL-2	Genital warts, sensitization dermatitis, malignant tumor, infection viral	Flu-like symptom, exanthematous dermatitis, severe toxic epidermal necrolysis, vascular leak syndrome, generalized edema, angioneurotic edema, urticaria, aggravate the primary lesion (such as psoriasis, eczema) or increase the risk of drug-induced hypersensitivity reactions [32,50,52,63,89-91]
IL-3	Marrow failure, aleukia, autologous bone marrow transplantation, immunoadjuvants	Flu-like symptom, minor erythematous reactions at the injection sites, urticaria [56]
IL-6	Immunodeficiency, malignant tumor, immunoadjuvants	Moderate injection-site reactions, maculopapular erythema, papulae, scale [58,72]
TNF-α	Malignant tumor, leukemia, bone marrow transplantation, cut down cholesterol	Flu-like symptom, local reactions [59-61].

Table 1: Indication of some cytokine products applied to clinical and the skin adverse reactions.

but less severe. Newton et al. [62] had reported a case of a 71-old male with renal cell carcinoma wide metastatic that received chemotherapy/biotherapy cycle which was 18 million units of IL-2 and 10 million units of IFN-α (administered by IV continuous infusion for 4 days) every three weeks. No skin complications occurred at the first treatment cycle. However, the patient started to present skin reaction after receiving the second course for 9 days, the skin was dry and flaky, and the lower extremities presented edema with a red lacy-like rash, accompanied with the sensation just like severe sunburn. Treated with furosemide 20 mg each day and external application drug (Eucerin cream), his skin had recovered 10 days later. It highly suggested that the skin reaction was induced by IL-2. Besides, erythematous dermatitis-like lesions might be the primary stage of some severe adverse reactions.

Serum sickness-like lesions

This kind of reactions includes fever, wheal, joint pain, lymphadenectasis, angioneurotic edema, urticaria, vasculitis and so on. Local indurations or necrotizing vasculitis can be found at the injection sites, and several distant cutaneous eruptions have been reported. GM-CSF can cause systemic wheal-like lesions. IFN-β1b can cause vascular inflammatory skin lesions. These reactions are common, but severities are unequal: range from local induration or pruritus to broad erythema, blisters and skin exfoliation of the whole body, even life-threatening reactions.

Severe adverse reactions

As mentioned above, severe toxic epidermal necrolysis, acute scalded skin-like adverse reaction after IL-2 therapy, exfoliative dermatitis associated with EPO, toxic epidermal necrolysis associated with G-CSF have been observed [52].

Secondary skin reactions

Cytokines may induce or aggravate autoimmune disorders, such as psoriasis, vitiligo, pyoderma gangrenosum, sarcoidosis, eosinophilic fasciitis, SLE, lichen planus, alopecia areata and so on. In some cases, IL-2 can induce fixed drug eruption of acetaminophen, tropisetron and ondansetron [63]. Ribavirin combined interferon therapy easily leads to drug eruption, of which distal eczema-like rashes are the most frequent. Besides, necrosis can occur at the injection site [13,64]. Pathological changes are predominantly the mononuclear cell infiltration in dermis, especially perivascular.

General Characteristics

Based on the current literatures, some characteristics of the adverse reactions could be summarized as follows:

- The severity is dose and duration dependent to some extent. However, sometimes, less dose of cytokines, even picogram can cause local or systemic physiological reaction. For example, the severity of vascular leak syndrome induced by IL-2 is dose-dependent, while the flu-like syndrome caused by IL-1 is quite universal whatever the dose.

- Be transitory and have the tendency of autotherapy which is closely related to the biologic activities of cytokines. As various cytokines can be influenced by each other in massive cytokine network,

and because of their very short half-life, it is usually reversible within 2-3 days after discontinued therapy. The adverse effects were usually mild, but sometimes the reactions were too severe to continue the treatment.

• Immune-mediated inflammatory protopathy or autoimmune diseases could be aggravated, for example, psoriasis, lichen planus, systemic lupus erythematosus, and so on.

• Influenza like symptoms (typically consisting of fever, fatigue, hypotension and tantrum) which probably resulting from the acute release of fever promoting factors in the hypothalamus are observed frequently.

• Local cutaneous reactions which may involve a local vascular inflammatory process or platelet dependant thrombosis at the injection sites are observed frequently.

• Polyethylene glycol (PEG)-containing product, seems to induce more frequent adverse reactions and a large number of side-effect cases related to combination therapy with ribavirin have been reported [65-69].

Mechanism

Cutaneous reactions have been frequently reported but poorly studied. Pathogenesis is thought to involve an imbalance in the TH1–TH2 cytokine equilibrium. The biological activities of cytokines take an important role in the occurrence of adverse reactions. The commonly postulated mechanisms involve either a direct toxic effect or an indirect immune-mediated effect. For instance, as a major stimulus, IL-2 can cause T cell proliferation and activation, which made active T cells produce various cytokines including IL-2 itself. Thus, the proliferation of T cell mediated by IL-2 is enlarged through a positive feedback mechanism. And the enlarged reactions of T cells to antigens resulting in antigen-mediated hypersensitivity or aggravated protopathy [70]. In addition, IL-2 can enhance the activity of natural killer cells, induce T lymphocyte-mediated cytotoxicity, and also promote B cells differentiation into plasma cells to generate antibodies. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) can cause exanthematous drug eruption at the injection sites, which is related to the efficacy of stimulating neutrophils clonal proliferation and aggregation. Otherwise, GM-CSF can cause the local infiltration of monocytes, neutrophils or eosinophils, which is relevant to its biological activity [71]. GM-CSF has also been shown to be an important factor in the recruitment and activation of Langerhans' cells in the skin. However, the exact mechanism of cutaneous reaction to GM-CSF remains speculative and may also involve the release of other cytokines or inflammatory mediators [72].

In addition, another significant factor is the impurities in biological products. The serum sickness-like reactions might be related to the purification process of human cytokines. As the confluent expression of some specified cytokines, the involvement of heterologous proteins may lead to serum sickness-like lesions at the injection sites. rhG-CSF can also cause erythematous dermatitis reactions. Sasaki et al. [73] have reported two cases of rhG-CSF induced drug eruption; the rashes are disappeared after replacing the production batch of rhG-CSF. According to this phenomenon it is considered that the skin reactions might not be concerned with the production of antibodies in the blood, but relevant with the impurities within the injection. It is interested that antibodies may not be detected in some typically cell-mediated reactions, such as eczematous reactions. Otherwise, as mentioned above novel long-acting PEG-containing drugs appear cause more adverse reactions [74]. Conversion to human cytokines is sometimes successful in patients with a poor tolerance to recombinant cytokine products. It is conceivable that PEG sensitize triggers of some reactions. Patch tests or intradermal tests may not reliable in some instance, as the allergen may be a metabolite rather than the drug itself [45].

Diagnosis and Treatment

Combining the history, rash type and characteristic, accurate clinical diagnosis can be made easily. Symptomatic treatment should be the chief point, such as application of anti-histamine preparations, topical glucocorticoid hormone cream or moisturizer. The cutaneous adverse reactions induced by cytokine are different from the traditional drug-induced dermatitis, because their occurrences and developments are related to biological effects of cytokine itself. So far, as immune modulators, cytokines have been applied in the clinical treatment of hypocytosis induced by chemotherapy, primary immunodeficiency or viral infection. However, with the advancement of gene engineering and a great clinical application of recombinant cytokine, such as the use of immunoloregulation therapy in some allergic diseases, many unpredictable adverse reactions will be encountered in clinic, which are required long-term observation and summarization. A good awareness of these reactions may be useful for a more accurate management of patient receiving the treatment. In addition, as a growing number of cases in relation to the adverse effects about biological response modifiers have been reported, clinicians are suggested to evaluate the merits and demerits before clinical medication of cytokines.

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