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Case Report
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Erythrodermic Onset of Atopic Dermatitis in a Patient with Multiple Myeloma: The Role of *Cytomegalovirus* Infection

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Abstract

Erythroderma is a generalized erythema and scaling involving >80% to 90% of the body surface area. It is due to generalization of pre-existing dermatoses, drug reactions, or cutaneous T-cell lymphoma, but identification of the underlying disease process represents one of the most complex challenges in dermatology. We present the case of a 66-year-old male with multiple myeloma who developed erythroderma. He reported no pre-existing dermatoses or allergies; he was recently started on valganciclovir, but there was no improvement despite its suspension. Furthermore, mites could not be identified from skin scraping examined microscopically, and a screening test panel for associated auto antibodies was negative. Histological examination of a 4-mm punch biopsy showed findings of paraneoplastic erythroderma, idiopathic erythroderma and atopic dermatitis. Tests for multiple myeloma showed no evidence of disease activity and a second biopsy excluded again a lymphoproliferative disease, thus we proposed a clinical diagnosis of atopic dermatitis.

The onset of erythroderma was associated with a cytomegalovirus reactivation twice, and the second time antiviral therapy resulted in improvement of erythema and itching. We believe that cytomegalovirus might have unleashed an erythrodermic onset of atopic dermatitis.

Keywords: Atopic dermatitis; Myeloma; Viral disease

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Introduction

Erythroderma is defined as generalized erythema and scaling involving >80% to 90% of the body surface area [1]. Some cases are also associated with erosions, crusting, hair, and nail changes [2]. Most commonly, it is due to generalization of pre-existing dermatoses (such as psoriasis or atopic dermatitis), drug reactions, or cutaneous T-cell lymphoma, but identification of the underlying disease process represents one of the most complex challenges in dermatology [1]. We present the case of a patient affected by multiple myeloma who developed erythroderma.

Case Presentation

A 66-year-old male with a medical history of multiple myeloma developed an erythematous rash spread over the entire skin surface, with scaling and itching. Dermatologic examination revealed extensive pink patches with feathering edges and large scaling on head, neck, trunk, and limbs (Figures 1, 2A, 2C, 2E). He did not report previous dermatoses or known allergies, but a history of xerosis. Regarding multiple myeloma, he achieved Very Good Partial Response (VGPR) after four cycles of Bortezomib-Thalidomide-Dexamethasone (VTD) induction therapy followed by Autologous Stem Cell Transplantation (ASCT). Laboratory tests showed eosinophilia (5500/mm^3), which has progressively increased for two months, until reaching a peak concomitantly with erythroderma. The previous month, acyclovir was replaced by valganciclovir for a cytomegalovirus reactivation (28000 copies/mL). Current blood tests found the presence of cytomegalovirus (481 copies/mL) and human herpesvirus-7 (90 copies/mL). The patient was started on oral prednisone and hydroxyzine, associated with topical steroids and emollients, but one month later erythroderma with lamellar scaling, intense itching and eosinophilia persisted, and thus a skin biopsy was performed. A week later, the patient developed fever, and blood cultures resulted positive for methicillin-susceptible *Staphylococcus aureus* and *Enterococcus casseliflavus*, therefore he received intravenous daptomycin in combination with piperacillin-tazobactam. Following the resolution of symptoms, all unnecessary drugs were suspended and intravenous 1 mg/kg/day dose of methylprednisolone was started, resulting in gradual improvement of erythroderma and eosinophilia. On the third day,

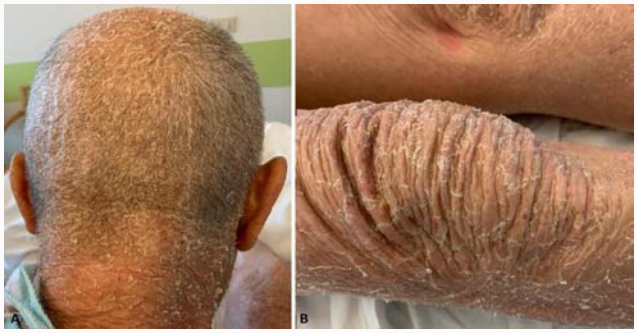

Figure 1: Dermatologic examination. Exfoliation of scale with underlying erythema and secondary excoriations on head (A) and knees (B).

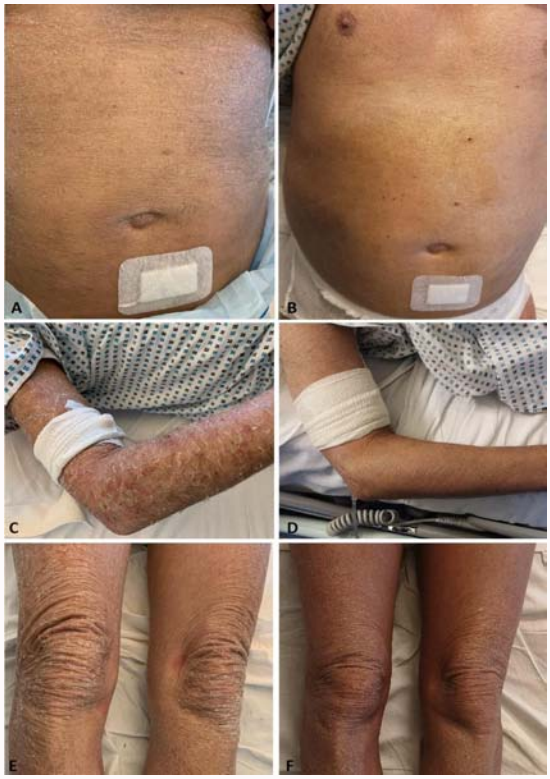

Figure 2: Dermatologic examination. Wide spread erythema with large thin scaling and excoriations (A, C, E). After the resolution of erythroderma, persistence of xerosis, lichenification and residual crusts (B, D, F).

as the patient developed a febrile relapse with positive blood cultures for *Klebsiella pneumoniae* Carbapenemase (KPC) enzyme producers, steroid therapy was suspended, and ceftazidime-avibactam treatment was set. Clinical improvement was again interrupted by a new febrile episode associated with reactivation of cytomegalovirus (16000 copies/mL) and worsening of erythroderma. Foscarnet therapy induced resolution of fever and reduction of erythema and itching. A further biopsy was performed, and intravenous methylprednisolone was started again. The pathologist concluded that histological and molecular findings were referable to a non-specific inflammatory reaction. After the resolution of erythroderma (Figures 2B, 2D, 2F) and negative viral tests, the patient was discharged with a follow-up program.

Discussion

Erythroderma is a condition caused by several etiologies that result

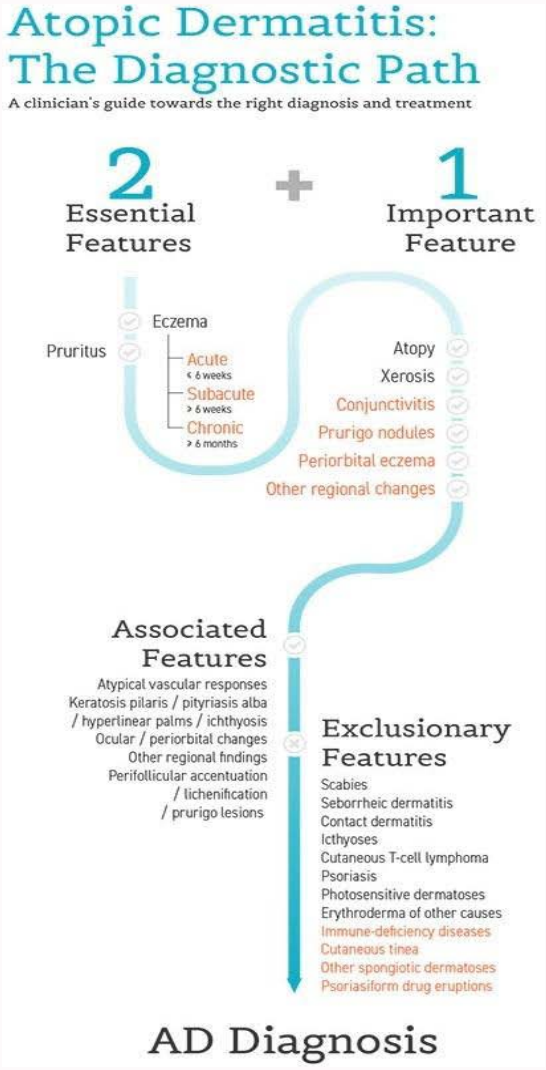

Figure 3: 2-Plus-1 AD diagnostic criteria proposed by Reynolds et al. [7].

in red inflamed skin on 80% to 90% or more of the body surface [1,2]. The diagnoses of the underlying systemic or cutaneous disease can be remembered with the mnemonic SCALPID: Seborrheic dermatitis/ sarcoidosis; contact dermatitis; atopic dermatitis/autoimmune diseases; lymphoma/leukemia; psoriasis/pityriasis rubra pilaris; infections (human immunodeficiency virus, dermatophytosis), ichthyoses, infestations (Norwegian scabies); drug reactions [2]. The most common disorders are contact dermatitis, atopic dermatitis, and psoriasis, along with drug reactions, while the most common malignancy is cutaneous T-cell lymphoma [2].

The color of the skin can vary from pink-red to red-brown to deep red-purple, and pruritus is observed in up to 90% of patients [1]. The onset of scaling is typically seen 2 to 6 days after the onset of the erythema [1,2]. It varies in size and color, depending upon the stage of the erythroderma and nature of the underlying disease: In more acute phases scales are usually large and crusted, whereas in chronic states they tend to be smaller and drier [1]. In cases of pre-existing dermatoses, nail changes may precede the erythroderma (e.g. pits in psoriasis or horizontal ridging in atopic dermatitis), whereas others develop subsequently, for example they can become thick, dry, and brittle [1,2]. Colonization of the skin with *Staphylococcus aureus* is common and can lead to secondary cutaneous infections as well as

bacteremia [1].

A detailed history is crucial for diagnosing the underlying etiology: Patients must be asked about pre-existing medical conditions, allergies, medications, and skin diseases (atopic or other dermatitis, psoriasis, etc) [2]. The presentation of erythroderma in individuals without a pre-existing skin disease is more common with drug-induced erythroderma or malignancy; compared with other causes, the onset of erythroderma secondary to medication is typically more sudden and rapidly progressing, the resolution is often quicker, and additional manifestations may be observed, like fever and peripheral eosinophilia, along with facial swelling, hepatitis, myocarditis, and allergic interstitial nephritis: This constellation of findings is referred to as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) [2]. Our patient reported no pre-existing dermatoses or allergies; he was recently started on valganciclovir, but there was no improvement despite its suspension, and eosinophilia already existed before. Furthermore, mites could not be identified from skin scraping examined microscopically, and a screening test panel for associated auto antibodies was negative, thus we performed a 4-mm punch biopsy. Histological examination showed parakeratosis, spongiosis, vacuolization in the basal layer, exocytosis of lymphocytes and granulocytes, inflammatory infiltrate in the dermis (with predominantly CD4+ T lymphocytes, histiocytes and granulocytes, but a moderate amounts of ezsinophils) and edema of the dermis.

Histological findings were compatible with paraneoplastic erythroderma, idiopathic erythroderma and atopic dermatitis [1]. Tests for multiple myeloma showed no evidence of disease activity, so we excluded this possibility. Erythroderma is labeled as idiopathic in 9% to 47% of cases (this group is composed mainly of older adult men with a chronic and relapsing course of pruritic erythroderma) and longitudinal monitoring of patients with idiopathic erythroderma may reveal undiagnosed cutaneous T-cell lymphoma [2], therefore we performed a second biopsy to enhance the accuracy of histopathologic diagnoses, but it excluded again a lymphoproliferative disease and showed a non-specific inflammatory pattern. Acute lesions of atopic dermatitis show spongiosis, intracellular edema in the lower epidermis, exocytosis of lymphocytes, a perivascular infiltrate of lymphocytes and macrophages around vessels of the superficial plexus, mast cells in different stages of degranulation, and occasional eosinophils [3]. The presence of dermal eosinophilic infiltrates is a characteristic histological feature observed in skin biopsies from patients with erythrodermic atopic dermatitis [4]. The diagnosis of atopic dermatitis remains clinical, as there is currently no reliable biomarker that can distinguish the disease from other entities: An elevated total and/or allergen-specific serum IgE level is not present in about 20% of affected individuals [5,6] as well as in our patient. Of all the existing diagnostic criteria, none are considered wholly or mutually exclusive in the diagnosis of atopic dermatitis, which remains prerogative of the clinician [7]. According to the 2-Plus-1 model (Figure 3) proposed by Reynolds et al. [7], our patient had two essential features (acute eczema and pruritus) and one important feature (xerosis), without any exclusionary features of atopic dermatitis.

Furthermore, the onset of erythroderma was associated with a *Cytomegalovirus* reactivation twice, and the second time antiviral therapy resulted in improvement of erythema and itching. We believe that cytomegalovirus might have been a trigger of the cell-mediated immune response that unleashed an erythrodermic onset of atopic dermatitis. Triggers (e.g. viral infections, food allergens, cosmetics, fragrance, weather, and other causes) are the leading cause of an atopic dermatitis exacerbation, and avoidance of triggers is an important mechanism patients can use to control disease activity [5]. Hafez et al. [8] found that active subclinical cytomegalovirus infection is more frequent in patients with atopic dermatitis and may have possible immunomodulatory role in the etiopathogenesis, even if it is not related to disease severity. Döcke et al. [9] suggest that active, subclinical cytomegalovirus infection is more frequent in patients with moderate to severe atopic dermatitis and may have immunopathological relevance [9]. In-spite of the high prevalence of cytomegalovirus infection and its potent immunomodulatory activities, the relation of cytomegalovirus to atopic dermatitis is still poorly understood [8,10].

Conclusion

Erythroderma is a dermatologic emergency that could necessitate hospital admission, therefore determining the underlying etiology is crucial, and any external aggravating factors must be eliminated. Specifically, any potential drugs inducing erythroderma must be stopped. Early diagnosis is paramount as it allows early treatment and prevention of erythroderma-associated morbidity and mortality. It is very important to recognize atopic dermatitis as a cause of erythroderma, especially in a patient with late onset of the disease and no personal or familial history of allergic diseases. Further studies are necessary to clarify the relationship between atopic dermatitis and cytomegalovirus infection.

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