Dermatology Practical & Conceptual

Stevens-Johnson Syndrome and Erythema Multiforme Induced by Imiquimod 5% Cream

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ABSTRACT

Introduction: Topical imiquimod is a safe and effective treatment for actinic keratoses, superficial basal cell carcinomas, and anogenital warts. The treatment is commonly associated with local inflammatory reactions, while systemic side effects are rare and generally mild. Only few cases of erythema multiforme and Stevens-Johnson syndrome have been described in association with topical imiquimod application.

Objective: We present a narrative review of the existing cases of erythema multiforme and Stevens-Johnson syndrome reported in the literature, analyzing the clinical appearance, the histology, and the treatment of the lesions.

Method: Twenty-one articles were retrieved. All the sourced articles were full-text reviewed to ensure that the contents were relevant to the study, which resulted in the exclusion of 10 articles.

Results: Nine case of erythema multiforme were reported, characterized by cutaneous rash, bullae, crusting, and erosive and targetoid lesions, mainly located at the extremities. Mucosal involvement and systemic symptoms were present in five and in three cases, respectively. Three cases of Stevens-Johnson syndrome were associated with topical imiquimod. In all cases, the authors reported targetoid lesions and areas of erosion affecting trunk and limbs, associated with systemic symptoms, and, in two cases, with mucosal erosions.

Conclusions: We hypothesize a possible role of interferon-γ, a cytokine involved in the pathogenesis of both herpes-associated erythema multiforme and Stevens-Johnson syndrome, which is released in response to the administration of imiquimod.

Introduction

Imiquimod is a toll-like receptor-7 agonist that acts as an immune response modifier by stimulating monocytes/macrophages and dendritic cells to produce cytokines that promote cellular immunity [1]. The topical formulation of imiquimod is approved for the treatment of actinic keratoses (AKs), superficial basal cell carcinomas (BCCs), and anogenital warts [2]. Moreover, off-label use of imiquimod cream has been reported as effective in other skin cancers, such as squamous cell carcinoma in situ and melanoma in situ [2].

Local skin reactions after the application of imiquimod are extremely common and include erythema, scabbing, induration, edema, erosion, flaking, ulceration, and vesicle formation, accompanied by itching, burning, and pain. On the contrary, systemic side effects are uncommon and generally mild; the most frequently reported ones are flu-like symptoms, myalgia, malaise, fatigue, fever, upper respiratory tract infections, sinusitis, and headaches [1]. Although the topical application of imiquimod is rarely associated with severe systemic side effects, sporadic cases of systemic drug reactions, including erythema multiforme (EM) and Stevens-Johnson syndrome (SJS), have been reported [3].

EM is an acute, self-limiting disease that is typically associated with hypersensitivity reactions to infections, in particular by herpes simplex virus and mycoplasma pneumoniae, or to drugs. EM has been further subdivided into EM minor and EM major according to the extent of the mucosal involvement [4].

SJS and toxic epidermal necrolysis (TEN) are potentially life-threatening mucocutaneous reactions, predominantly drug induced. In EM and SJS, skin detachment affects less than 10% of the body surface area (BSA), while TEN is characterized by an involvement of over 30% of the skin surface. Involvement between 10% and 30% of BSA is defined as SJS/TEN overlap [5].

Historically, EM major, SJS, and TEN have been considered part of the same disease spectrum; however, due to their distinct morphological characteristics, EM major and SJS are currently accepted as separate entities [5].

Objectives

This narrative review aimed to summarize the current understanding of severe systemic drug reactions caused by the topical application of imiquimod and to offer some insight on the potential pathogenetic mechanism of such reactions.

Methods

We performed a literature search using the PubMed database using the following search terms: “imiquimod”, “erythema multiforme” and “Stevens-Johnson syndrome”. Additionally, we reviewed references from relevant original papers to identify further eligible studies not covered by the original database search. Criteria for inclusion of the studies for the review were as follows: articles in English; case reports; use of imiquimod for in-label indications. A total of 21 articles were retrieved. All the sourced articles were full-text reviewed to ensure that the contents were relevant to the study, which resulted in the exclusion of 10 articles.

Results

We found 11 studies related to EM and SJS occurring in patients treated with imiquimod 5% for BCCs or AKs, for a total of 12 case reports, published from 2010 to 2024 (Table 1).

Imiquimod cream was applied 2–5 times a week for BCCs and 2–3 times a week for AKs (Table 1).

Nine cases of EM associated with imiquimod 5% were described, both during treatment of BCCs [3,6-9] and of AKs [9-12]. Clinical manifestations appeared after an average of 21 days after having started treatment with imiquimod 5% and were characterized by maculopapular rash [8-10], maculopustular rash [3,7], maculovescicular rash [3,9,12], bullae [9,10], crusting, and erosive and atypical targetoid lesions [6,7,9,11] frequently involving extremities and associated with systemic flu-like symptoms [3,6,10]. Mucosae were also involved in 5/9 cases, with stomatitis [7,9,11], conjunctivitis [3,7], and erosions of the nose [7]. The scheme of application of imiquimod 5% in patients was twice a week [9], three times a week [3], or five times a week [6-8] for patients with BCCs and twice a week [9,11] or three times a week [6,10,12] for patients with AKs. Skin biopsy was performed in 6/9 cases and was characterized by keratinocyte necrosis and intraepidermal vesiculation affecting the epidermis, accompanied by an inflammatory lymphohistiocytic infiltrate in the papillary dermis [3,6-8,10,12]. These reactions were managed with imiquimod interruption [3,6-12], systemic [3,7,9,11] or topical corticosteroids [7,8,12], opical [6] or oral antibiotics [7,11]. The lesions started to improve after between a few days and up to 15 days and were completely resolved after a maximum of 21 days. Only one patient had a past history of HSV infection, but he denied any recent flares [11].

SJS associated with imiquimod 5% cream was previously described in three patients. All patients were treated with imiquimod 5% for BCCs and SJS symptoms starting 8–42 days from the beginning of the treatment. All patients presented targetoid lesions and areas of erosion affecting trunk and limbs [13-15], associated with systemic symptoms such as malaise [13,15], hypotension [13], tachycardia [14], and fever [13,14]. Mucosal lesions were present in 2/3 cases

Table 1. Review of the Literature.

Authors	Age	Sex	Comorbidity	Site of BCC/ AK	Scheme of Application of Imiquimod	Time of Appearance of EM/ SJS After Application of Imiquimod	Skin Lesions	Sites of Lesions	Mucous Involvement	Systemic Involvement	Treatment	Time of Resolution
Erythema Multiforme												
Garcia-Arpa et al. (2010)	66	F	Hypertension, depression, osteoarthritis	BCC cheek, AK nose/ upper lip	3 times weekly for AK, 5 times weekly for BCC	35 days	Areas of crusting that left erosions when lifted, and round erythematous papules, some with erosion, some with target morphology	Chest, forearms, hands, legs	No	Fever, malaise	Imiquimod discontinued, topical antibiotics	A few days
Ballester et al. (2014)	70	M	Hypertension	AK scalp, nose	3 times weekly	21 days	Maculopapular eruption, bullae	Elbows, knees, palms, soles	No	Flu-like syndrome	Imiquimod discontinued	15 days
Chan et al. (2017)	66	M	Hypertension, hypercholester-olemia	BCC on anterior chest	5 times weekly	21 days	Macular and pustular eruption	Widespread	Stomatitis and conjunctivitis	No	Betamethasone valerate 0.1% ointment	NK (complete resolution at 12 weeks)
Chan et al. (2017)	79	M	Chronic lymphocytic leukemia	BCC on right upper back	NK	6 days	Acral atypical target lesions	Extremities	Stomatitis and nasal erosions	No	Prednisone, nystatin and roxithromycin	NK (complete resolution at 6 weeks)
Yanes et al. (2017)	60	M	No	AK scalp	twice weekly	14 days	Targetoid lesions	Extremities	Stomatitis	No	Oral prednisone, fluocinonide mouthwash, oral clindamycin	14 days
Pena-Lopez et al. (2017)	56	F	Gorlin syndrome	BCC nose	5 times weekly	28 days	Erythematous-edematous papules and plaques	Dorsum of the hands, forearms, arms, ankles	No	No	Imiquimod discontinued, mometasone furoate on nose	15 days

Table 1 continues

Table 1. Review of the Literature. *(continued)*

Authors	Age	Sex	Comorbidity	Site of BCC/AK	Scheme of Application of Imiquimod	Time of Appearance of EM/SJS After Application of Imiquimod	Skin Lesions	Sites of Lesions	Mucous Involvement	Systemic Involvement	Treatment	Time of Resolution
Maxfield et al. (2019)	83	M	NK	2 BCC shoulder, AK left wrist right dorsal hand	twice weekly	7 days	Macules, patches, plaques, vesicles, bullae, targetoid lesions	Extremities	Stomatitis	No	Imiquimod discontinuation, oral prednisone	21 days
Camacho Molina et al. (2020)	84	M	Hypertension, atrial fibrillation	BCC temporal	3 times weekly	28 days	Macular and pustular/vesicular eruption	Trunk, arms	Conjunctivitis	Malaise, fever, dysphagia, cough	Imiquimod discontinued, EV methylprednisolone	21 days
Trčko (2020)	77	M	No	AK scalp	3 times weekly	21 days	Symmetrically distributed macular and vesicular eruption	Arms, neck	No	No	Imiquimod discontinued, topical corticosteroids	20 days
Stevens-Johnson syndrome												
Leitner et al. (2016)	NK	F	NK	BCC chest	NK	42 days	Atypical targetoid lesions, later erosions Nikolski + on 20% BSA	Trunk, arms, extremities	No	Malaise, hypotension, fever	Hospitalization, imiquimod discontinued, intensive skin care	NK
Tedman et al. (2020)	65	F	Hyperlipidemia	BCC left forearm and hip	NK	10 days	Blistering eruption	Central chest, forearm	Conjunctivitis, stomatitis	Fever, tachycardia	Imiquimod discontinuation, hospitalization, intensive skin, mouth and eye care	7 days
Trave et al. (2024)	79	M	Hypertension, benign prostatic hyperplasia	2 BCC chest	5 times weekly	8 days	Targetoid lesions, erosions	Trunk, face, arms, extremities	Stomatitis, genital erosions	Malaise, fatigue	Imiquimod discontinuation, oral prednisone, intensive skin care	20 days

Abbreviations: AK: actinic keratosis; BCC: basal cell carcinoma; BSA: body surface area; EM: erythema multiforme; NK: not known; SJS: Stevens-Johnson syndrome.

and affected the mouth [14,15], conjunctiva [14], and genitals [15]. A skin biopsy was performed in 2/3 cases [13, 14], which showed full-thickness epidermal necrosis and inflammatory infiltrates. Two patients with SJS were hospitalized [13, 14] and one was managed at home with systemic steroids [15]. In all cases, imiquimod was discontinued and intense skin care was started [13-15]. The lesions resolved in 7–20 days [14,15].

In all case reports, a detailed drug history was obtained, and possible alternative causes of SJS and EM, such as infections and new medications, were excluded.

Discussion

The clinical presentation and evolution of EM and SJS caused by topical imiquimod does not differ from classic forms caused by systemic drugs. EM cases were characterized by localized target lesions, with predominant acral localization, and SJS cases were mainly characterized by non-palpable atypical targetoid lesions that predominantly affected the trunk [5]. In both EM and SJS, limited areas of erosion and crusting were described. Both EM major and SJS are characterized by mucosal involvement, but, unlike EM, SJS is generally accompanied by systemic involvement such as fever, malaise, fatigue, and other flu-like symptoms [16]. Interestingly, in one of the reported SJS cases, mucosal involvement was absent. However, the systemic and cutaneous involvement were severe, so the case was still included.

Systemic drugs are a well-recognized cause of EM and SJS, particularly antibacterial drugs, rifampicin, barbiturates, anti-inflammatory agents, thiazide diuretics, anticonvulsants, and vaccines. On the other hand, SJS and EM have been rarely associated with topical treatments. In most cases, the culprit drug was applied on mucosal membranes, such as antibiotic eyedrops [17,18], mesalazine enema [19,20], and antibiotic intranasal cream [21]. Cases of SJS and EM following the cutaneous application of drugs other than imiquimod seemed much rarer and were mostly associated with extensive skin damage [22], like in a case of topical application of nitrogen mustard in a patient with mycosis fungoides [23]. Imiquimod appears to represent an exception, and, to the best of our knowledge, the pathogenetic reasons for this exception have not yet been investigated.

The pathogenesis of SJS and EM is complex and likely determined by a dysregulation of cell-mediated immunity resulting from a combination of genetic predisposition and exogenous triggering factors [24]. Numerous cytokines and chemokines have a role in promoting these conditions. The increase in interferon gamma (IFN-γ), a cytokine produced by T lymphocytes, is probably involved in the pathogenesis of herpes-associated EM and SJS/TEN, mainly by inducing overexpression of major histocompatibility complex on keratinocytes, which makes them more susceptible to the action of T CD8+ cytotoxic lymphocytes [24]. Since imiquimod induces the release of IFN-γ [25], this drug may itself be particularly likely to cause EM or SJS. The reported rarity of this occurrence could be related to the topical route of administration and minimal systemic absorption of imiquimod [26]. However, the above-hypothesized mechanism may represent an exception, since IFN-γ has been reported as involved in herpes-associated EM, while tumor necrosis factor alpha (TNF-α) is expressed in drug-induced EM lesions [27].

We hypothesize that an increased systemic absorption caused by the application of the drug could raise the risk of systemic reactions, including EM and SJS. For instance, in Italy, topical imiquimod can be prescribed for superficial BCCs, which are often ulcerated lesions [28] inducing a higher systemic absorption. In addition, as 4/9 cases of EM and 3/3 cases of SJS were associated with the treatment of two or more BCCs or AKs, it can be hypothesized that the application of the drug in a wider area of skin may increase the risk of systemic absorption and drug reaction. Moreover, all authors reported an intense local inflammatory reaction preceding or contemporary to the diagnosis of EM and SJS, a factor which may favor systemic absorption through vasodilation and increased vascular permeability, predisposing the patients to systemic reactions. The diagnoses of EM and SJS were based on clinical features in all reports and supported by histology in eight cases. In all case reports, a detailed drug history was obtained, and possible alternative causes of SJS and EM, such as infections and new medications, were excluded.

The management of EM and SJS was vastly different in various case reports, especially in EM, where topical and systemic antibiotics and steroids were often prescribed. Due to the severity of the clinical manifestations, it is important to be aware of the possibility of EM and SJS caused by topical imiquimod and to provide suspected cases with standard treatment: culprit drug interruption accompanied by supportive care including skin care and symptom control, with the possible addition of immunomodulatory drugs such as corticosteroids, cyclosporine, and intravenous immunoglobulins in SJS [29].

Conclusions

In conclusion, EM and SJS caused by topical imiquimod are a rare but reported occurrence. Nonetheless, we believe that clinicians should be mindful of such a possibility and be ready to manage it appropriately. Further studies are needed to investigate the pathogenesis of imiquimod-mediated EM and SJS, particularly pertaining to the role of IFN-γ.

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