Publisher's Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. Dermatology Reports is, therefore, E-publishing PDF files of an early version of manuscripts that undergone a regular peer review and have been accepted for publication, but have not been through the copyediting, typesetting, pagination and proofreading processes, which may lead to differences between this version and the final one. The final version of the manuscript will then appear on a regular issue of the journal. E-publishing of this PDF file has been approved by the authors.

Stevens-Johnson induced by imiquimod 5% cream: a case report

Ilaria Trave,1,2* Ilaria Salvi,1,2* Claudia Micalizzi,1,2 Riccardo Castelli,1,2 Aurora Parodi,1,2 Emanuele Cozzani1,2

1Department of Dermatology, Dipartimento della Salute (DiSSal), University of Genoa; 2IRCCS, Ospedale Policlinico San Martino, Genoa, Italy

*These authors share first authorship.

Correspondence: Ilaria Trave, via A. Pastore 1, Genoa, 16132.
Tel.: +39.0105555750.
E-mail: ilaria.trave@unige.it

Key words: imiquimod; Stevens-Johnson syndrome; adverse drug reaction.

Contributions: all the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Ethical approval and consent to participate: this study was conducted in accordance with ethical guidelines.

Availability of data and material: all data supporting the findings of this study are available within the article.

Consent for publication: the patient gave his consent to use his personal data for the publication of this case report and any accompanying images.
Abstract
Imiquimod 5% cream is an approved treatment for actinic keratoses, superficial basal cell carcinomas and anogenital warts. Severe systemic side effects associated to imiquimod 5% cream are rare, although few cases of erythema multiforme and Stevens-Johnson syndrome have been described. We present a case of Stevens-Johnson syndrome associated to topical treatment with imiquimod of two superficial basal cell carcinomas.

Introduction
Imiquimod is a synthetic compound and a member of the imidazoquinolone family, which acts as a toll-like receptor agonist. It is an immune response modifier which stimulates the patient’s innate and adaptive immune responses (1). It is approved for the topical treatment of actinic keratoses (AKs), superficial basal cell carcinomas (BCCs) and anogenital warts (2). Side effects are common and are mostly local reactions which include itching, burning, bleeding, vesicles, erosions, ulcerations, excoriations, crusting, induration, edema and pain. Mild systemic side effects, such as upper respiratory tract infections, flu-like symptoms, sinusitis and headaches, are uncommon (1). Severe systemic side effects in patients treated with imiquimod 5% are rare and acute reactions, such as erythema multiforme (EM) and Stevens-Johnson syndrome (SJS), are considered exceptional (3). We present a case of Stevens-Johnson syndrome associated to treatment with imiquimod 5% cream.

Case report
A 79-year-old male with a history of hypertension and benign prostatic hyperplasia presented himself to the emergency department with cutaneous and mucous lesions accompanied by malaise and fatigue. He had been recently visited by a dermatologist who prescribed treatment with 5% imiquimod cream for two superficial BCCs, on his anterior and posterior chest. He was advised to apply imiquimod daily for 5 times a week for 6 weeks but the treatment was interrupted after six applications of the drug. Physical examination revealed target lesions on arms, legs, palms and soles of his feet and some less erythematous, crusted and eroded lesions on his trunk and face. He also had erosive lesions in his mouth and genitals. The areas treated with imiquimod showed an intense inflammatory reaction with crusting and erosion (Figure 1). Overall, the erosions affected less than 10% of the total body surface area (BSA). The patient refused to undergo a skin biopsy. Serum herpes simplex antibodies were negative. The diagnosis of SJS was based on the typical clinical presentation reported above. Since
no new drugs had been recently introduced, imiquimod was identified as the culprit drug with a Naranjo ADR probability score of 6.

The patient was recommended to interrupt the treatment with imiquimod and to start oral therapy using prednisone 37.5 mg/day and careful skincare.

After twenty days since the diagnosis of SJS, the lesions had almost completely disappeared, leaving no scars (Figure 2). Prednisone was gradually tapered and interrupted after two weeks.

Discussion and Conclusions

SJS and toxic epidermal necrolysis (TEN) are two dermatologic conditions representing a spectrum of the same disease, characterized by widespread epidermal necrosis and sloughing of skin. Systemic symptoms (fever, malaise, cough) can be associated, and they generally precede the cutaneous manifestations. Mucosal involvement is also typical, especially involving the oral mucosa, while ocular and genital involvement are less frequent. The classification of the disease is based on body surface area (BSA) involvement: while SJS is defined by a more localized involvement (< 10% BSA), a diagnosis of TEN is made when over 30% of BSA is affected. Nonetheless, both SJS and TEN have high morbidity and mortality, and require prompt treatment. In most cases, SJS is caused by drugs, infections are the second most common cause (4). Several differential diagnoses should be considered, including pemphigus vulgaris, linear IgA bullous dermatosis, staphylococcal scalded skin syndrome (SSSS), and erythema multiforme major (EMM). In particular, since the histopathologic presentation of SJS and EMM are similar, the diagnosis must be based on clinical features (4).

Attempts have been made at classifying the two diseases according to clinical presentation, for example, in 1993, Bastuji-Garin et al. proposed an illustrated atlas as a tool for standardizing the diagnosis (5). According to these criteria, the typical targetoid lesions on the palms and soles of our patient could be more indicative of EMM. However, the presence of flat atypical targets, macules and larger areas of epidermal detachment suggested a diagnosis of SJS. Moreover, according to the review by Frantz et al. the localization on the trunk, mucosal involvement of two sites and lack of infective trigger favor the diagnosis of SJS.

In the vast majority of cases, the culprit drug is systemic, however, a small number of cases of SJS caused by topical medication have been reported, such as cases triggered by the ophthalmic application of ofloxacin (6) and moxifloxacin (7) and one case of SJS following the application of topical mesalazine (8).

Moreover, very few cases of SJS related to topical imiquimod have been reported in the literature. SJS associated to imiquimod 5% cream was previously described in 2 patients. Leitner et al (9) reported the case of a female patient treated with topical imiquimod for a BCC on the chest. After 42
days of treatment, the patient developed atypical targetoid lesions on the trunk and both arms, accompanied by malaise. She was hospitalized with hypotension and fever. The rash progressed into confluent erosions with positive Nikolsky sign covering 20% of the body surface, without mucosal involvement. The diagnosis of SJS was confirmed by skin biopsy, that showed full thickness necrosis and inflammatory infiltrates with eosinophils. The lesions improved and resolved with imiquimod withdrawal and intensive skin care.

Tedman ad al. (10) presented the case of a 65-year-old female who developed a blistering eruption involving the central chest and forearms 10 days after beginning a treatment with 5% imiquimod cream for BCCs of the left forearm and hip. She presented mucosal (oral ulcers and conjunctivitis), and systemic (fever and tachycardia) involvement. The patient was managed with imiquimod discontinuation, hospitalization and intensive skin, mouth and eye care, achieving complete symptomatic improvement in 7 days. Histological examination showed focal parakeratosis, apoptotic keratinocytes, and full-thickness epidermal necrosis. There was a subepidermal split leading to bulla formation. The superficial dermis contained pigment-laden macrophages and a mixed inflammatory infiltrate.

In contrast with previous cases, our patient was not hospitalized due to his personal preference, thus we offered frequent outpatient visits in the clinic. Moreover, the treatment with oral steroids proved effective, and could be easily managed at home.

In conclusion, SJS is an exceptional complication of treatment of skin cancer with topical imiquimod. A high level of suspicion can lead to early recognition of the disease, and to prompt management, leading to a positive outcome.

References


Figure 1. Appearance of lesions at baseline. Inflammatory reaction with erosion of the areas treated with imiquimod (a), target lesions on palms (b), erosive lesions of the tongue (c).
Figure 2. Appearance of lesions after 20 days. Healing of the target lesions on palms (a), resolution of the erosions on the tongue (c).