Dermatol Ther (Heidelb) (2023) 13:1909–1934
https://doi.org/10.1007/s13555-023-00978-0

REVIEW

Rare Cutaneous Side Effects of Imiquimod: A Review on Its Mechanisms, Diagnosis, and Management

Xiaoyan Zhang · Yao Xie · Lin Wang

Received: April 29, 2023 / Accepted: July 5, 2023 / Published online: August 1, 2023

ABSTRACT

As an immune-response modifier, imiquimod can bind to Toll-like receptors on immune cells and enhance innate and adaptive immune responses, exerting potential antitumor and antiviral effects, which led to its approval by the US Food and Drug Administration for the treatment of actinic keratosis, superficial basal cell carcinomas, and anogenital warts, and to its off-label use in treating many other benign and malignant dermatoses. Although topical administration of imiquimod has been considered well tolerated, an increasing number of cutaneous and noncutaneous side effects are being reported as its clinical applications expand. This review primarily focuses on rare cutaneous side effects. To the best of our knowledge, this is the first article to summarize the mechanism, diagnosis, and management of rare cutaneous side effects of imiquimod, which may help to heighten awareness among physicians, especially dermatologists, about potential imiquimod-induced cutaneous side effects.

X. Zhang · Y. Xie · L. Wang (✉)
Department of Dermatovenereology, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu 610041, Sichuan, China
e-mail: lkzwl@126.com

Keywords: Imiquimod; Rare; Cutaneous side effects; Mechanism; Diagnosis; Management

Key Summary Points

Imiquimod is approved by the US Food and Drug Administration for the topical treatment of anogenital warts, superficial basal cell carcinomas, and actinic keratosis.

Off-label use of imiquimod for the treatment of many other benign and malignant dermatoses is becoming increasingly common.

Although imiquimod is considered to be a safe drug and is generally well tolerated, an increasing number of rare cutaneous side effects, such as vitiligo, pemphigus, psoriasis, and lichen planus, are being reported.

Most of these rare cutaneous side effects are reversible, but a few are irreversible or even fatal.

Dermatologists should be vigilant about the potential side effects of imiquimod, and regular follow-up is crucial to detect potential risks during and after treatment.

INTRODUCTION

Imiquimod [1-(2-methylpropyl)-1,*H*-imidazo(4,5-*c*)quinoline-4-amine], an immunomodulating agent of the imidazoquinoline family, was developed by 3M Pharmaceuticals Saint Paul in the US [1]. Imiquimod was originally developed as a nucleoside analog, and its activity was discovered during the search for new anti-herpes virus drugs [2–4]. It was first approved by the US Food and Drug Administration (FDA) for the topical treatment of anogenital warts in patients 12 years and older in February 1997 [2], and later (in 2004) for superficial basal cell carcinomas (sBCC) and actinic keratosis (AK) [5]. Recently, there have been increasing reports of the treatment of other diseases benefiting from the off-label application of imiquimod, indicating its important potential in treating skin tumors and infectious diseases [6, 7]. Due to its hydrophobicity and molecular size (Mr = 240.3), imiquimod has the property of percutaneous permeation, making it suitable for topical use, which offers patients a noninvasive and nonsurgical treatment modality for skin diseases [3, 8–10]. Imiquimod is marketed in two concentrations, 5% and 3.75%, with the former being more widely used [1].

Despite widespread investigation of imiquimod's mechanism of action, it is still unclear due to its pleiotropic effects on a variety of diseases. Imiquimod plays its potential antitumor and antiviral roles primarily by directly or indirectly enhancing innate and acquired immune responses, which result in the recognition and killing of tumor cells or virus-infected cells [11]. As a synthetic Toll-like receptor (TLR) agonist, imiquimod can bind to TLR7 and, to a lesser degree, to TLR8 on antigen-presenting cells, which leads to the activation of nuclear factor kappa-B (NF-κB) via the myeloid differentiation factor 88 (MyD88)-dependent pathway, ultimately promoting target cell maturation and increasing the levels of various proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interferon (IFN)-α, interleukin (IL)-6, IL-8, and IL-12, as well as chemokines, including CCL2, CCL3, and CCL4 [8, 12]. These cytokines, on the one hand, enhance innate immunity, and, on the other hand, induce the transformation of T cells into a T helper 1 (Th1) phenotype, which facilitates cell-mediated immune responses by stimulating the secretion of IFN-γ from naive T cells [10]. In addition, imiquimod can enhance acquired immunity by activating plasmacytoid dendritic cells (pDCs), a unique immune cell subgroup that highly express TLR7/9 and are responsible for producing type I IFNs, namely, IFN-α and IFN-β. The interaction between imiquimod and TLR7 on pDCs results in the activation of the TLR7/MyD88 signaling pathway and, consecutively, the robust production of type I IFNs, which is essential for innate immune responses as well as for the Th1 polarization pattern [1, 13].

In addition to the TLR-dependent pathway, imiquimod has been shown to enhance inflammatory responses by interacting with adenosine receptors [14]. Also, it has been confirmed that imiquimod at high concentrations directly induces apoptosis in tumor cells in vitro and in vivo by activating the endogenous pathway [10, 15]. Furthermore, the therapeutic role of imiquimod is partly due to its antiangiogenic effect. Imiquimod induces the production of IFNs, IL-10, and IL-12, leading to the downregulation of some proangiogenic factors, vascular endothelial cell apoptosis, and the inhibition of vascular movement and invasion [8, 10].

RARE IMIQUIMOD-ASSOCIATED CUTANEOUS SIDE EFFECTS

The pleiotropic effect of imiquimod makes it an effective treatment for many dermatological conditions. With increasing depth of research, the off-label use of imiquimod for the treatment of other diseases, such as herpes simplex [16], lentigo maligna [11], vulvar Paget's disease [17], cutaneous leishmaniasis [18], primary cutaneous anaplastic large cell lymphoma [19], and folliculotropic mycosis fungoides [20], is becoming increasingly common. In most of the literature, imiquimod is considered to be a safe drug and is generally well tolerated. Currently,

the most common cutaneous adverse effects are dose-dependent local reactions, such as erythema, erosion, edema, flaking, scabbing, and excoriation at the application sites, which is attributed primarily to the direct immunomodulation effects of imiquimod on the skin, and recovery is achieved after discontinuation or a reduction in use [1, 21, 22]. Intense local reactions tend to result in better results for treatment [10]. However, with the widespread application of imiquimod, there have been an increasing number of reports about its rare cutaneous side effects, such as vitiligo, psoriasis, erosive pustular dermatosis, and erythema multiforme [23–26]. Some systemic adverse effects, including nausea, diarrhea, influenza-like symptoms, and arthralgia, have also been reported [10, 27]. In this review, we mainly focus on the skin diseases induced by imiquimod and attempt to discuss the potential underlying reasons for them with the aim of improving the understanding of these possible side effects and their management. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Vitiligo or Vitiligo-Like Hypopigmentation/Depigmentation

Although application-site vitiligo and vitiligo-like hypopigmentation/depigmentation are listed on the package insert as possible side effects, there is not much literature available on them. In 2005, Brown et al. [28] reported the first case of hypopigmentation at the treated site due to topical imiquimod treatment of condyloma acuminatum. To date, only approximately 30 cases have been reported. Imiquimod-induced vitiligo and vitiligo-like hypopigmentation/depigmentation have been reported to occur subsequent to topical treatment for genital warts (condyloma acuminatum) [28–38], BCC [39–43], periungual verruca vulgaris [44], extramammary Paget's disease [45], melanoma or metastatic melanoma [24, 46], AK [47], and radiation keratosis [48]. Only one case of pigment loss during or after the treatment of AK has been reported [47], as the frequency of treatment for AK is twice a week according to the FDA-indicated regimen, which is lower than the frequency of treatment for BCC (five times a week for 6 weeks) and genital warts (3 times a week for a maximum of 16 weeks) [49]. In addition, the concentration of imiquimod used to treat AK is 3.75%. According to the literature, the time between the initial application of imiquimod and the onset of pigmentary changes has a wide range of 4 weeks to 11 months. Almost half of the patients suffered from hypopigmentation/depigmentation after 3 months of administration. Therefore, regular follow-up at short intervals is conducive to the early detection of lesions.

Pigment loss is often localized to the site of treatment and sometimes affects nontreated adjacent or distant sites. In a report by Edgar et al. [44], the patient was treated externally with 5% imiquimod cream three times weekly for the left thumb and right fifth digit but developed depigmented patches on the bilateral dorsal hands and right foot. Similarly, Alatabani et al. [31] reported a case of a patient who experienced depigmentation at both the treated and nontreated sites after topical treatment of genital warts with imiquimod 5% cream. Serra et al. [36] reported an interesting case in which, in addition to hypopigmentation at the sites of application, the patient developed halos of hypomelanosis around multiple preexisting melanocytic nevi of the trunk following topical administration of imiquimod for vulvar condylomata. In these reports, patients denied using any topical treatment other than imiquimod.

The majority of the patients who have been reported refused histopathological confirmation of diagnosis by a biopsy from the depigmented or hypopigmented areas. Thus, the diagnosis of vitiligo was usually made based on the clinical presentation of lesions, or the term "depigmentation" or "hypopigmentation" was used to describe the white patches. In 2009, a biopsy-confirmed case of imiquimod-induced vitiligo was reported by Gowda et al. for the first time [39]. Since then, only a few patients have undergone biopsy. A reduction or absence of melanin and melanocytes was found in the white patches but not in the adjacent normal

skin [37, 39, 45, 46, 48], which was consistent with the clinical manifestations.

Some of the mechanisms underlying imiquimod-induced pigment changes have been extensively investigated. However, its detailed mechanism has still not been clarified. It is not possible for imiquimod to result in depigmentation or hypopigmentation by local irritation because some patients have undergone irritation several times, such as through cryotherapy [28, 32, 37, 45], podophylline application [45], electrodesiccation [37, 39], and exposure to a CO_2 laser [30], prior to topical treatment with imiquimod without presenting such a rash. An alternative view posits that the pathogenesis might be related to benzyl alcohol, a chemical component of imiquimod cream, which is thought to be a predisposing factor for vitiligo [43]. At present, the mechanism of action of imiquimod is generally accepted to be involved in the pathogenic effects. As we mentioned above, imiquimod can stimulate TLR7, inducing the release of proinflammation cytokines, e.g., TNF-α, IFN-α, IL-6, and IL-12, which are closely related to the pathogenesis of vitiligo and vitiligo-like hypopigmentation [40, 50]. Moreover, the Th1 signal pathway is evoked and in turn increases the perilesional infiltration of $CD8^+$ and $CD4^+$ cytotoxic T cells; the latter produce IFN-α and IL-2, which contribute to the genesis of vitiligo and promote the conversion of $CD8^+$ cells into cytotoxic T cells via stimulation by IL-12 [50]. Moreover, imiquimod could induce apoptosis of melanocytes by upregulating the expression of caspase-3 and mitogen-activated protein kinase and downregulating B-cell lymphoma-2 [51]. In summary, imiquimod leads to a loss of function and a decrease in the number of melanocytes directly or indirectly.

Hypopigmentation or depigmentation is typically irreversible and may even spread. A few studies have reported varying degrees of repigmentation after discontinuation of imiquimod [32, 46] or the topical use of 0.03% or 0.1% tacrolimus ointment [30, 31, 37]. Thus, when mild depigmentation occurs, prompt discontinuation and topical tacrolimus ointment may be beneficial to improve the prognosis. In addition, of the cases reported thus far, one patient had a family history of vitiligo, and one patient suffered from nonsegmental vitiligo [32, 47], indicating that topical imiquimod may act as a triggering factor for patients with a family or personal history and should be prescribed with more caution.

Psoriasis

Psoriasis is a T-cell-mediated and chronic inflammatory skin disorder [52]. The etiology is not well defined, and some exogenous factors can trigger psoriasis. It has been confirmed that exposure to drugs, such as imiquimod, is an important risk factor that can trigger psoriasis [53]. Although imiquimod-treated mice are one of the most commonly used models for studying psoriasis, rare clinical cases of imiquimod-induced psoriasis have been reported. Furthermore, imiquimod might exacerbate preexisting psoriasis [13].

We retrieved ten cases described as imiquimod-induced or imiquimod-exacerbated psoriasis (summarized in Table 1), which has been reported following treatment of AK [54, 55], BCC [56], and condyloma acuminatum [57] in adults and the off-label treatment of molluscum contagiosum and verruca plana in children [58]. The reported cases included three males, six females, and one whose sex was not mentioned. Most patients (6/10) had no personal or family history of psoriasis. In the remaining cases, the psoriasis was stable and well controlled, with scattered rashes or even no rashes, thus requiring only infrequent use of topical corticosteroid; in those cases, the topical administration of imiquimod provoked a widespread flare, indicating that imiquimod may be a precipitating trigger for the relapse or exacerbation of psoriasis [26].

The morphological types of imiquimod-induced psoriasis include psoriasiform eruptions, psoriasis guttata, psoriasis vulgaris, and psoriatic erythroderma [13, 55, 59]. The skin manifestations are similar to those of classical psoriasis and are characterized by erythematosquamous plaques which can develop at the sites of imiquimod application and/or generalized regions distant from the treated areas.

Table 1 Summary of published cases of psoriasis induced or exacerbated by topical imiquimod

Case	Age (years), gender	Personal history of psoriasis	Indication for imiquimod	Sites of psoriatic eruption	Clinical manifestation	Pathology	Diagnosis	Treatment	Outcome
Gilliet et al., 2004 [13]	58, M	No	Psoriasis	Back, trunk, and lower extremities	Enlarged erythematous plaque surrounded by small erythematous satellite lesions and distant, droplet-like lesions	Parakeratosis, acanthosis, focal loss of the granular layer, and papillomatosis	Psoriasis guttata	Topical corticosteroids and NB-UVB therapy	Prompt regression
Wu et al., 2004 [60]	58, M	Yes	sBCC	Trunk and limbs	Small erythematosquamous plaques	Epidermal hyperplasia, Munro microabscesses, lymphocyte infiltrate	Psoriasis	Topical calcipotriol and mometasone furoate	Resolved after 8 weeks
Rajan et al., 2006 [59]	64, F	Yes	sBCC	Limbs, trunk, and face	Small plaques of psoriasis appearing	Features consistent with psoriasis	Psoriasis	Topical steroid and calcipotriol	Slowly improved after 10 weeks
Fanti et al., 2006 [26]	77, M	Yes	AK	Scalp, trunk, face, and limbs	Small erythemato-scaling plaques	NR	Psoriasis	None	Resolved after 4 weeks
Patel et al., 2011 [56]	74, M	No	AK	Scalp, face, trunk, and extremities	Erythematous, scaly, well-defined plaques	Concordance with diagnosis of psoriasis	Psoriasis	Topical clobetasol and NB-UVB	Improved after a few months
Smith et al., 2013 [58]	5, F	No	MC	Anterior neck (application site)	Well-defined, geographic, red plaque with overlying white scale	NR	Psoriasiform reaction	Topical triamcinolone	Resolved after 2 weeks
Smith et al., 2013 [58]	6, NR	No	VP	Medial canthus (application site)	NR	NR	Psoriasis	Topical hydrocortisone and desonide	Awaiting follow-up
Tsutsumi et al., 2017 [55]	78, F	No	AK	Glabella, trunk, and extremities	Isolated erythemas accompanied by whitish scales	Epidermal parakeratosis, hypogranulosis, vacuolar degeneration, perivascular infiltration of lymphocytes and eosinophils	Psoriasis	Oral infliximab (5 mg/kg)	Improved dramatically

Table 1 continued

Case	Age (years), gender	Personal history of psoriasis	Indication for imiquimod	Sites of psoriatic eruption	Clinical manifestation	Pathology	Diagnosis	Treatment	Outcome
Igari et al., 2019 [54]	89, F	No	AK	Forehead, trunk, and extremities	Erythematous scaly lesions	Epidermal hyperplasia, parakeratosis, subepidermal dilated capillaries, lymphocyte infiltrate	Psoriasis	Topical corticosteroids	Moderate effectiveness
Nakamura et al., 2022 [57]	26, F	Yes	CA	N/A	Exacerbation of the psoriasis plaques and distal interphalangeal joint pain and mild swelling	NR	Psoriatic arthritis exacerbated by topical imiquimod	Topical calcipotriene and betamethasone dipropionate and oral apremilast	Resolved

M male, *F* female, *AK* actinic keratosis, *LM* lentigo maligna, *sBCC* superficial basal cell carcinoma, *CA* condyloma acuminatum, *MC* molluscum contagiosum, *VP* verruca plana, *NB-VUB* narrowband ultraviolet B phototherapy, *NR* not reported, *N/A* not applicable

The involvement of distant, previously normal skin may be attributed to low-level systemic absorption of topical imiquimod, which is supported by the evidence that mild lymphopenia, a known side effect related to systematic imiquimod treatment, was found in a patient who suffered from the generalized psoriatic lesions beyond the sites of imiquimod administration [60]. One patient developed fingernail abnormalities, which manifested as onychodystrophy, oil spots, and longitudinal ridging [56]. Only two patients were reported to suffer from pruritus, which is an important symptom in classic psoriasis [54, 56].

The histopathological features of imiquimod-induced or imiquimod-exacerbated psoriasis are largely consistent with those of classic psoriasis, e.g., parakeratosis, focal granular layer loss, acanthosis, occasional Munro microabscesses, and perivascular infiltration of lymphocytes in the upper dermis [13, 54, 55, 60]. Although dermal eosinophil infiltration and lichenoid patterns are considered to be clues to the diagnosis of drug-induced psoriasis [53], they were found in only one patient [55].

Most patients responded well to topical treatment with corticosteroid ointment and/or calcipotriol cream and narrowband ultraviolet B phototherapy (NB-UVB) [13, 26, 54, 56, 58, 60]. In one patient, the eruptions resolved spontaneously without any treatment after 4 weeks [26]. Only one patient was treated with infliximab, a monoclonal antibody against TNF-α, due to the poor response to the combined treatment of topical calcipotriol, oral etretinate, and psoralen plus ultraviolet A (PUVA), which led to erythroderma [55]. Unlike classic psoriasis, which is prone to relapse, no recurrence of imiquimod-induced psoriasis has been reported, indicating that this disorder may be transient.

Multiple mechanisms likely underly psoriasis induced or exacerbated by imiquimod. As a TLR7 agonist, imiquimod binds to TLR7 on pDCs and thereafter induces the production of a large amount of IFN-α, leading to T-cell activation and specifically the activation of Th1 and Th17 cells, which is strongly associated with the onset and development of psoriasis [13, 56]. Furthermore, Tsutsumi et al. [55] reported a case of imiquimod-induced psoriasis in which the

eruptions resolved with a decrease in TNF-α levels after infliximab treatment, indicating that TNF-α also plays an important role in psoriasis associated with imiquimod. In addition, the levels of mast cells, which release various cytokines that trigger psoriasis, can be increased in lesions after the use of topical imiquimod [54, 61]. Furthermore, the exacerbation of preexisting psoriasis may be partly attributed to the tissue-resident memory T cells [57].

Erythema Multiforme and Stevens–Johnson Syndrome

Erythema multiforme (EM) is an acute, immune-mediated, and usually self-limiting disease that is generally categorized into EM minor and EM major depending on the presence or absence of mucosal involvement [62]. Among the main triggers of EM, infection is the most common, followed by systematic drugs and, most commonly, antibiotics, nonsteroidal anti-inflammatory drugs, and antiepileptics [63]. Very little has been described about EM induced by topical drugs, and even less literature exists about EM induced by topical imiquimod. Stevens–Johnson syndrome (SJS) and EM were previously thought to be part of the same disorder spectrum but are now considered separate disease entities due to different precipitating factors, clinical manifestations, treatments, and prognoses [63]. Only one case of SJS triggered by imiquimod has been reported [64], which is described together with EM in this section.

Almost all reported patients with EM or SJS suffered from intense local irritation at application sites, e.g., erythema, pus, crusting, and erosions, which may result in an improved therapeutic efficacy. According to the literature, the clinical and histopathological features of drug-related EM may differ little from those of nondrug-related forms of EM. These patients mainly exhibited multiple round erythematous patches, macules, and plaques, some of which showed vesicular centers or central clearing, namely, target lesions. The lesions were predominantly distributed symmetrically on the extremities, including the palms and soles, and the trunk was also involved in some patients. Mucosal involvement, including stomatitis, conjunctivitis, and erosions or ulcers of the nostrils and lips, was found in half of the patients [23, 65–67]. Patients diagnosed with imiquimod-induced SJS presented with lesions similar to those observed in patients with EM and obvious mucosal involvement and systematic symptoms, such as fever and tachycardia [64]. Histopathologic findings included keratinocyte necrosis, intraepidermal blistering, interface dermatitis, and inflammatory cell infiltration in the upper dermis, which were consistent with EM [65, 68].

The disease severity may be related to the frequency and total doses of imiquimod applied and the degree of local reaction, so low doses of imiquimod are recommended in cases of widespread or very large lesions [69]. Once suspicious EM eruptions occur, imiquimod should be discontinued immediately. Some patients recovered soon after discontinuation [65, 68]. Administration of corticosteroids topically or systematically contributed to the resolution of the rash [62].

The exact mechanism of how this occurs is currently unknown. One perspective is that the intense local reaction at application sites before EM may lead to an impaired skin barrier, which promotes the systematic absorption of imiquimod and facilitates the inflammatory response underlying the pathogenesis of EM [23, 68]. An alternative view suggests that this adverse reaction appears to be associated with systematic cytokine release triggered by imiquimod through the TLR-7 pathway instead of the systematic absorption of imiquimod [69]. These cytokines, particularly TNF-α, IFN-α, IL-6, and IL-8, can enhance the Th1-cell-mediated immune response, which plays an important role in the initiation of EM [65]. There is also the opinion that the occurrence of EM is attributable to the combined action of the two mechanisms mentioned above [68]. The detailed mechanism remains to be further studied in the future.

Table 2 Summary of published cases of lupus-erythematosus-like reactions induced by topical imiquimod

Case	Age (years), gender	Indication for imiquimod	Clinical manifestation	Pathology	DIF	IHC	Autoantibodies	Diagnosis	Treatment	Outcome
Barr et al., 2011 [21]	78, M	AK	Ulcerated plaque	Interface dermatitis, perivascular and periadnexal lymphocytic infiltration	NR	CD3, CD4, CD8, CD20(+)	NR	SCLE–like changes	NR	NR
Chan et al., 2011 [78]	91, F	LM	Depigmentation	Interface dermatitis, perivascular and perifollicular lymphocytic infiltration, no mucin and basement membrane thickening	NR	CD3, CD20, CD56 (+)	NR	LE-like reaction	NR	NR
Chan et al., 2011 [78]	75, M	AK	Papules with dark crusts	Interface dermatitis, perivascular lymphocytic infiltration	NR	NR	NR	LE-like reaction	NR	NR
Maguiness et al., 2015 [71]	50, F	BCC	Erythematous to violaceous annular and polycyclic plaques	Interface dermatitis, perivascular and periadnexal lymphocytic infiltration, dermal mucin deposition	NR	CD123(+)	ANA (−) Anti-Ro/La (−)	SCLE-like change	NR	Resolved
Jiménez-Gallo et al., 2017 [80]	69, F	AK	Irregular erythematous plaques, whitish hyperkeratoses	Interface dermatitis perivascular and periadnexal lymphocytic infiltration, dermal mucin deposition	IgM, IgG, fibrinogen (+)	NR	ANA (+) Anti-histone (+)	CLE	Oral hydroxychloroquine	Resolved
Fernández et al., 2018 [77]	68, M	NR	Erythematous plaque, telangiectasias	Interface dermatitis, perivascular and periadnexal lymphohistiocytic infiltration, no mucin, thickening of the basement membrane	NR	NR	NR	LE-like reaction	Topical mometasone followed by tacrolimus	Resolved

Table 2 continued

Case	Age (years), gender	Indication for imiquimod	Clinical manifestation	Pathology	DIF	IHC	Autoantibodies	Diagnosis	Treatment	Outcome
Giraud et al., 2020 [76]	41, F	AK	Erythematous scaly macules with arthralgias	Interface dermatitis, perivascular and perifollicular lymphocytic infiltration	IgG, IgM, C3, C1q (+)	NR	ANA (+) Anti-dsDNA (+)	SLE	Oral hydroxychloroquine and topical corticosteroids	Mild recurrence in summer and persistence of autoantibodies
Giraud et al., 2020 [76]	78, F	BCC	Erythematous, annular rash	Interface dermatitis, lymphocytic infiltration without perivascular or periadnexal tropism	(−)	NR	ANA (−) Anti-Ro/SSA (+)	LE-like reaction	Topical corticosteroids	Resolved
Safadi et al., 2022 [81]	82, F	AK and suspicious BCC	Hyperkeratotic plaque	Epidermal hyperplasia, lymphocytic infiltration, dermal mucin deposition	NR	CD123(+)	NR	HLE-like reaction	Topical mupirocin and halcinonide	Resolved

M male, *F* female, *AK* actinic keratosis, *LM* lentigo maligna, *BCC* basal cell carcinoma, *LE* lupus erythematosus, *SCLE* subacute cutaneous lupus erythematosus, *CLE* cutaneous lupus erythematosus, *HLE* hypertrophic lupus erythematosus, *DIF* direct immunofluorescence, *IHC* immunohistochemistry, *ANA* antinuclear antibody, *ds-DNA* anti-double-stranded DNA, *NR* not reported

Table 3 Summary of published cases of lichen planus induced by topical imiquimod

Case	Age (years), gender	Indication for imiquimod	Imiquimod regimen	Interval time (weeks)	Sites of lichenoid eruption	Clinical manifestation	Pathology	Diagnosis	Treatment	Outcomes
O'Mahony et al., 2010 [112]	21, M	GW	NR	13	Shaft, glans, and prepuce	Multiple violaceous plaques with Wickham striae	NR	LP	Plastic surgery and circumcision	Excellent remission
Wang et al., 2013 [30]	37, M	GW	Every other night, 3 months	4	Coronal and foreskin areas	Multiple purple-red specks	Wedge-type thickening of granular layer, liquefied degeneration, and lymphocyte infiltration	LP	PDT	Complete remission
Brown et al., 2014 [111]	88, F	BCC	2 times/ week, 3 weeks	3	Inside of the lower lip, right buccal mucosa, and right lateral border of the tongue	Erythema, ulcers, and leukoplakic whitish lesions	No	Lichenoid reaction to imiquimod	Oral prednisone (60 mg)	Complete remission
Drummond et al., 2015 [115]	64, F	BCC	NR	NR	Scalp	Large erythematous plaque	Loss of hair follicles, diffuse scarring of the superficial derma and band-like infiltrate of lymphocytes	Lichen planopilaris	NR	NP
Zhao et al., 2020 [113]	33, M	GW	3 times/ week, 3 months	13	Prepuce and shaft of the penis	Irregular, slightly elevated, well-defined, pale and reddish plaques	Wedge-shaped hypergranulosis, lymphocyte infiltrate and pigment incontinence	LP	Topical 0.1% tacrolimus	Improved markedly
Zhao et al., 2020 [113]	53, M	GW	3 times/ week, 2 months	8	Penis and scrotum	Many flat-topped violaceous plaques with Wickham striae	Wedge-shaped hypergranulosis, lymphocyte infiltrate and pigment incontinence	LP	Topical 0.1% tacrolimus	Improved markedly
Furuoka et al., 2020 [114]	73, F	AK	3 times/ week, 4 weeks	8	Left cheek	55 × 70 mm in size, slightly elevated reddish plaque	Liquefaction degeneration, lymphocyte infiltrate and pigment incontinence	Lichenoid drug reaction	Topical 0.1% tacrolimus	Resolved

Table 3 continued

Case	Age (years), gender	Indication for imiquimod	Imiquimod regimen	Interval time (weeks)	Sites of lichenoid eruption	Clinical manifestation	Pathology	Diagnosis	Treatment	Outcomes
Domingues et al. 2012 [116]	44, M	Oral LP	4 times	4	Lips, arms, and legs	Erosion and white papules with Wickham striae	No	Imiquimod reactivation of LP	Topical clobetasol	Resolved gradually

M male, *F* female, *GW* genital warts, *AC* actinic cheilitis, *AK* actinic keratosis, *BCC* basal cell carcinoma, *LP* lichen planus, *PDT* photodynamic therapy, *NR* not reported

Spectrum of Lupus Erythematosus-Like Reactions

Long-term treatment with certain drugs may lead to drug-induced lupus (DIL), an idiosyncratic adverse drug reaction [70]. According to a previous report, approximately 10% of lupus erythematosus (LE) cases are caused by drugs, mainly via systemic delivery [70, 71]. It is generally known that a significant association has been found between mutations in TLR signaling and the initiation and/or exacerbation of LE in both humans and mouse models [72]. Upregulation of TLRs, specifically TLR7, contributes to the development of LE [73]. Furthermore, SLE patients have higher blood levels of IFN-α, which is mainly produced by pDCs and is associated with disease activity and severity [74]. As a TLR7 agonist, imiquimod can stimulate TLR7 and lead to the accumulation of pDCs in application sites, inducing the substantial production of IFN-α. Therefore, imiquimod can trigger the occurrence of LE-like reactions, but this has not been widely reported.

To date, nine cases of LE-like reactions to imiquimod have been reported in the literature (summarized in Table 2), and more than half (6/9) of these patients were female patients, which may be due to imiquimod inducing much higher levels of IFN in women than in men [75]. One patient was diagnosed with systemic lupus erythematosus (SLE) that manifested as erythematous scaly macules with arthralgias and positivity for autoantibodies [76], and the remaining cases were cutaneous LE. The clinical manifestations of reported cases had high diversity. Some patients presented with the typical rash of LE, which is characterized by well-circumscribed scaly erythematous papules [71, 76, 77], while the presentation in some patients was entirely different. Chan et al. [78] reported two cases of LE-like reactions following topical imiquimod treatment; one manifested as pigmentation, and the second manifested as papules with dark crusts. The patient reported by Barr and coworker presented with ulcerated plaque [21]. This diversity may be due to different dosages and/or durations of imiquimod application and different stages of disease [78].

The histological findings have not been well defined due to the small number of cases. Interface dermatitis (ID), which is characterized by vacuolar changes/liquefaction, necrotic keratinocytes (Civatte bodies), and infiltration of lymphocytes [79], was found in the majority of previously reported cases [21, 71, 77, 78, 80]. However, ID can be observed not only in patients with autoimmune connective tissue diseases but also in patients with immune reactions against drugs, viruses, and tumors [21, 78, 79]. Furthermore, the microscopic features of LE, e.g., hyperkeratosis, epidermal atrophy, follicular and acrosyringeal plugging, and dermal perivascular and/or periadnexal lymphocytic infiltration, were not uncommon in imiquimod-induced cases. Although the absence of dermal mucin deposition and/or basement membrane thickening was regarded as beneficial for distinguishing between true LE and imiquimod-induced lupus reactions [21, 78], this finding is not specific due to the increased mucin levels or moderately thickened basement membrane observed in other patients [71, 77, 80, 81]. Thus, it is possible to misdiagnose these histological features as true LE without a clinical history of topical imiquimod administration [78]. Additionally, anti-CD123 immunohistochemical staining was positive in two cases, indicating the accumulation of pDCs in skin lesions, which was consistent with the mode of action of imiquimod [71, 81]. Circulating autoantibodies, including antinuclear antibody (ANA), anti-double-stranded DNA (dsDNA), anti-histone, and anti-SSA, were detected in three patients [71, 76].

Due to the diversity of clinical manifestations and pathological changes in patients with LE induced by imiquimod, the clinicopathologic correlation, appropriate clinical details, and other laboratory examinations are essential for an accurate diagnosis. Unlike true LE, all reported outcomes were good except for that of the patient diagnosed with SLE with a mild recurrence in summer, indicating that the LE-like reaction to imiquimod is reversible, and signs and symptoms disappear after withdrawal of imiquimod. Therefore, anti-inflammatory drugs are not recommended [70].

Pemphigus

Pemphigus is a group of rare and potentially life-threatening autoimmune disorders that are clinically characterized by erosions and intraepidermal blisters involving skin and/or mucous membranes [82, 83]. Although the etiology of pemphigus is currently elusive, the loss of keratinocyte adhesion caused by anti-desmoglein 1 (Dsg1) and/or anti-desmoglein 3 (Dsg3) autoantibodies seems to account for intraepidermal blisters and acantholysis [83, 84]. Several factors, including genetic and exogenous factors, can elicit the initiation or exacerbation of pemphigus. Among the recognized exogenous predisposing factors, drugs are the most common trigger [84, 85]. Long-term systemic IFN-α treatment could induce pemphigus by stimulating the production of antiepidermis antibodies, most commonly the pemphigus type, by autoreactive B cells [86–88]. Thus, as an inducer of IFN-α production, imiquimod may indirectly induce the upregulation of pemphigus autoantibodies and subsequent development of pemphigus [22]. In 2003, Campagne et al. [22] reported the first pemphigus-like lesions induced by topical imiquimod, which was used to successfully treat vulvar intraepithelial neoplasia in a 27-year-old woman. To date, only eight cases have been reported, including one that involved a 5-year-old child (summarized in Table 3). The clinical variants included pemphigus foliaceus [89, 90], pemphigus vulgaris, pemphigus vegetans [91], and a pemphigus-like reaction [88].

The clinical manifestations of imiquimod-induced pemphigus included versicles, bullae, and erosions, which corresponded to the pathological findings, characterized by intraepidermal acantholytic blisters [22, 91, 92]. It is difficult to distinguish pemphigus induced by imiquimod from the idiopathic variant from a clinical or pathological perspective. Inquiring repeatedly about the past medication history is impotant.

Lesions in reported cases developed at application sites and/or distant sites in a timeframe of 2–8 weeks. Systemic absorption of imiquimod or substantial cytokine synthesis may be responsible for distant involvement

[92]. Campagne et al. [22] considered that this side effect may be dose independent. However, in the study of Bauza and coworkers, the pemphigus-like lesions did not recur after an imiquimod dose reduction from 500 to 250 mg/day [92]. In addition, imiquimod treatment leading to the flare-up of preexisting pemphigus was reported in one patient, which may be attributed to the overproduction of some cytokines induced by imiquimod binding to TLR. Most of these cytokines, such as IFN-α, TNF-α, IL-1, and IL-6, are related to the activity of the disease [93]. Thus, imiquimod could cause disease relapse by amplifying the disease activity [87]. One patient was subjected to human leukocyte antigen (HLA) molecular typing, revealing DR7, DR14, and DQ1 phenotypes, which are known to be related to the genetic predisposition [91]. In such genetically predisposed individuals, low levels of preexisting circulating autoantibodies, in combination with a cytokine environment induced by imiquimod therapy, may facilitate pemphigus development [83].

Moreover, immunodiagnostic tests, including direct immunofluorescence (DIF) and serological detection of autoantibodies, are particularly useful to diagnose pemphigus and differentiate the various diseases [94]. In six patients who underwent immunodiagnostic tests, DIF and autoantibody (Dsg1 and/or Dsg2) tests were positive in two cases and negative in two cases. One patient was diagnosed with atypical pemphigus vulgaris due to the detection of non-Dsg autoantibody [83].

Unlike the chronic course of pemphigus, the initiation and flares of pemphigus induced by drugs are commonly short-lived, with a quick recovery and no recurrence after stopping the culprit drug [85, 87, 90]. Despite this, all reported patients with symptoms related to imiquimod had undergone additional treatments for weeks to months, which mainly included systemic corticosteroids and/or topical steroids. One patient received 3 years of topical and systemic corticosteroid treatment [89]. Further studies involving more cases will be needed to show whether such patients require aggressive treatment because long-term administration of corticosteroids would result in serious side effects.

Pityriasis Rubra Pilaris

Pityriasis rubra pilaris (PRP) is a rare and chronic inflammatory disease with a clinical and pathological similarity to psoriasis and an unknown etiology. It has occasionally been reported that drugs, trauma, and infection events may trigger this disorder [95]. PRP in association with topical imiquimod has been reported in four patients, including one patient with PRP that was misdiagnosed as AK aggravated by imiquimod treatment [96].

The time interval between the initiation of imiquimod and PRP onset ranged from 2 to 5 weeks. Patients manifested with the typical PRP rash characterized by generalized erythematous-orange papulosquamous lesions, usually with unaffected skin and palmar and/or plantar keratoderma. The pathological examination of four patients showed the characteristics of classic PRP, including hyperparakeratosis alternated with orthokeratosis in both the horizontal and vertical directions, psoriasiform epidermal hyperplasia, and superficial perivascular lymphocytic infiltrates [96–99]. Of note, intraepidermal acantholysis was found in all patients and was thought to be a pathological indicator that differentiates PRP from psoriasis [100].

All patients achieved a good prognosis after discontinuation of imiquimod and receiving treatments. Two patients responded well to oral acitretin [97, 98]. Oral methotrexate led to complete remission in one patient [97]. Another patient improved significantly after narrowband UVB therapy, but the skin lesions did not regress completely at 7 months after the start of medication [99]. Topical and/or oral corticosteroids showed no effectiveness in patients with PRP induced by imiquimod [96, 97, 99]. The duration of treatment varied, with the longest time being 26 months [96].

The enhanced Th1 proinflammatory cytokine pathway and systematic circulation of proinflammatory cytokines induced by imiquimod may be involved in the pathogenesis of PRP related to imiquimod [97].

Erosive Pustular Dermatosis of the Scalp

As a rare chronic inflammatory skin disease, erosive pustular dermatosis of the scalp (EPDS) commonly occurs in elderly male individuals with atrophic sun-damaged skin and is associated with local trauma, e.g., surgery, cryotherapy, radiotherapy, and medications [101–103]. Topical imiquimod treatment has been reported to be responsible for the occurrence of EPDS [102].

To date, five patients have been reported to be diagnosed with EPDS after topical imiquimod treatment for AK of the scalp (four cases) or squamous cell cancer (SCC) of the scalp (one case). All reported patients were older men aged from 74 to 84 years, with an average age of 81.4 years. The dermatological manifestations were characterized by the association of erythema, pustules, erosion, and crusts involving the photodamaged and/or bald scalp. The pathological findings were nonspecific and revealed epidermal atrophy, focal erosion, pustular dermatitis, and mixed dermal infiltration [102].

EPDS might be overlooked and easily misdiagnosed as other diseases, such as bacterial or fungal infections, pemphigus, skin cancers, pustular psoriasis, and pyoderma gangrenosum due to the absence of specific laboratory tests and pathognomonic histologic features [102–104]. A misdiagnosis of EPDS might lead to incorrect treatment, e.g., 5-fluorouracil, imiquimod, or cryotherapy, which could aggravate the condition [103]. Critical clues that aid in the diagnosis of EPDS induced by imiquimod include medication history, clinical manifestations of erosions, sterile pustules and crusts on the previously sun-damaged scalps of older patients, a negative microbiological test and DIF, and a good response to steroids [101, 102, 104]. In addition, it is important to distinguish EPDS from an obvious local reaction related to imiquimod. The former usually lasts for months and does not resolve spontaneously without treatment, while the latter resolves rapidly following the withdral of imiquimod [104].

Four patients achieved complete resolution after treatment, and the treatment and prognosis were not mentioned for one patient. Two patients were treated with topical clobetasol [102], one patient was treated with oral prednisone [104], and the other received topical dapsone therapy [105]. Topical or systemic steroids have been considered the first-line treatment for EPDS; however, they are not always effective [105, 106]. Furthermore, topical steroids could result in more skin atrophy, which is strictly related to the development of EPDS [104]. Thus, alternative treatments with equal treatment efficacy and fewer side effects have been reported, such as topical tacrolimus, photodynamic therapy, and topical dapsone [101, 105].

The mechanism by which imiquimod induces EPDS remains unclear. It has been confirmed that photodamaged skin expresses increased proinflammatory factors which lead to the onset and maintenance of the immune-mediated reaction [107, 108]. As an immune modifier, imiquimod might further amplify and prolong the immune response when used to treat skin tumors at sites of photodamage by inducing an enhanced inflammatory reaction [102, 108].

Lichen Planus and Lichenoid Reaction

Lichen planus (LP) is a chronic immune-mediated inflammatory disease that commonly involves the skin and mucous membrane and is mostly idiopathic [109]. Lichenoid reaction (LR) shares most of its clinical and histopathological characteristics with LP and can be triggered by drug exposure [110]. Therefore, Brown and coworkers [111] suggested that some previously reported cases of imiquimod-induced LP should be described as LR. As a rare adverse effect of topical imiquimod, LP and LR have been reported in eight patients, including one case of LP in a patient misdiagnosed with solar cheilitis who had a recurrence of LP after four applications (summarized in Table 3).

It is well established that LP is characterized by cytotoxic immune reactions induced by type I IFN [112]. Keratinocytes expressing particular antigens, such as viral, pharmacological, or self-

antigens, are attacked and destroyed by inflammatory cells [111, 112]. Imiquimod interacting with TLRs could increase the production of IFN-α and other cytokines and thereafter activate cytotoxic T cells, which may be an etiological factor in the cases of LP or LR induced by imiquimod.

Local administration of imiquimod triggered the first occurrence of LP or LR following treatment for genital warts [30, 112, 113], AK [114], BCC [115], and actinic cheilitis [111]. The average latent period between the drug initiation and the onset of eruptions ranged from 3 to 13 weeks, with a median of 7.6 weeks. Unlike idiopathic LP, which is mostly symmetrically distributed on the lateral sides of the extremities, imiquimod-induced LP and LR commonly develop at and/or near the treated sites [111]. Morphologically, they present with erythematous to purple, flat-topped papules or plaques that are similar to idiopathic LP. Wickham striae were found in three patients [112, 113, 116]. Involvement of other mucosal sites was not observed in these patients. Microscopic findings were characterized by overlying keratinization, basal cell liquefactive degeneration, and a band-like layer of lymphocytic infiltrate along the dermoepidermal junction.

The lichenoid drug eruptions were less likely to spontaneously resolve and did not regress even after ceasing the causative drug [117]. Therefore, in addition to the discontinuation of imiquimod, another treatment was needed. Three patients responded well to tacrolimus ointment, a calcineurin inhibitor which has been shown to inhibit T-cell activation and the production of several cytokines, including IFN-α [113, 114]. One patient was successfully treated with 60 mg of prednisone [111]. Another patient had undergone plastic surgery and circumcision because the condition was aggressive and did not respond to steroid treatment [112].

Telogen Effluvium

The development of hair follicles is a dynamic and cyclic process which determines hair growth and shedding and includes the growing phase (anagen), remodeling phase (catagen), and quiescent phase (telogen) [118, 119]. Hair follicles stay in the telogen phase when their growth cycle is disrupted by some triggers, e.g., drugs, stress, surgery, and chronic inflammation, resulting in diffuse hair loss, which is called telogen effluvium [120–122]. To date, only three cases of hair loss related to the topical application of imiquimod have been reported [3, 122].

Although all cases were imiquimod induced, the routes of administration and clinical manifestations were different. One patient developed localized alopecia at the treated site after treatment with topical imiquimod for SCC in situ on the scalp [123]. In the other two cases, diffuse hair loss occurred after self-application of vaginal suppositories (containing 6.25 mg imiquimod) for the treatment of cervical intraepithelial neoplasia [122]. Both of these patients suffered from severe systemic adverse effects related to imiquimod treatment, including fever, fatigue, headache, and flu-like symptoms, during the treatment period. A positive pull test and increased ratio of telogen to anagen hairs may aid correct diagnosis. There is a general view that drug-induced telogen effluvium is typically seen 2–3 months after the initiation of treatment [124]; however, all patients presented an obvious increase in hair loss approximately 15–16 weeks after commencing imiquimod, indicating that doctors should extend the time to 3–4 months prior to the start of hair loss when looking for a trigger and other potential causes should be excluded. Imiquimod-triggered telogen effluvium was reversible and resolved 5–7 months after the discontinuation of imiquimod.

No recent literature has explored the mechanism. Enhanced local or systemic immune responses induced by imiquimod that disrupt the growth cycle of hair follicles may account for this finding. Paradoxically, a study revealed that when imiquimod is applied during mid- and late telogen, hair follicle stem cells are activated, inducing hair follicles to enter the growing phase in advance [125]. Furthermore, imiquimod was used to treat alopecia universalis, and transient hair growth was

observed in a 15-year-old girl [126]. Thus, further studies are warranted.

Skin Tumors

The goal of reducing unnecessary surgery and associated costs has led researchers to focus on topical applications for skin cancer treatment. Imiquimod exerts an outstanding antitumor effect by enhancing innate and acquired immune responses and has been prescribed to treat various benign and malignant skin tumors, such as BCC, lentigo maligna, Paget's disease, primary cutaneous anaplastic large cell lymphoma, and folliculotropic mycosis fungoides, with promising clinical results. However, with the expansion of the scope of application, imiquimod has been reported to paradoxically induce skin tumors at the treated sites, which necessitates hypervigilance.

Eruptive Epidermoid Cysts

Epidermoid cyst (EC), a benign cutaneous tumor, originates from the follicular infundibulum and is related to the abnormal healing of the infundibular epithelium following follicular inflammation. The application of imiquimod induces local inflammation secondary to the cytokine cascade reaction, including the overproduction of IL-1α, which intensely stimulates the aberrant keratinization of the infundibulum and the production of abnormal keratin, resulting in pilosebaceous duct obstruction and thus the development of EC [127–129].

In all nine cases reported previously, eruptive epidermal cysts appeared after treatment with imiquimod (5 times/week, 6–12 weeks) for BCC, indicating that EC is a rare side effect of imiquimod treatment for BCC. The patients presented with verrucous plaques studded with bright or whitish papules with/without central pores at application sites. Skin biopsy specimens revealed that the cysts located in the middle dermis were filled with multiple infundibular keratins and were lined by stratified squamous epithelium [127]. No pathological proof of BCC was observed in these biopsy specimens after imiquimod treatment. Thus, EC is not only a local immune reaction but also a typical remission pattern in specific anatomical regions, namely, seborrhoeic areas of the face [25]. Additionally, Diluvio et al. [25] highlighted the role of dermoscopy in the diagnosis of EC, which was characterized as a popcorn-like hyperkeratotic yellow-whitish lesion formed by the coalescence of multiple elements [25]. Among the reported cases, five resolved spontaneously without treatment after 6 months [127], and two patients responded well to topical retinoids [130, 131].

Keratoacanthoma

As a low-grade cutaneous tumor, keratoacanthoma (KA) grows rapidly and has the potential for spontaneous regression [132]. KA is known to usually arise secondary to skin trauma, scarring, and laser treatment and has rarely been reported following topical imiquimod treatment for AK, Bowen disease, and superficial BCC [133–135]. One patient has received renal transplantation, and this immunosuppressive condition is conducive to KA development [133, 136]. The lesions developed at the application sites and presented with solitary or multiple nodules and papules with/without a central keratin plug. Pathological pictures revealed a keratin-filled crater-shaped area lined by squamous epithelium. Cellular atypia and some mitotic figures make it difficult to distinguish KA from SCC; however, rapid development is one of the important clues to the correct diagnosis of KA [134]. One patient underwent surgical resection and no recurrence was observed in 6 months [133]. In another case, almost all lesions resolved spontaneously in 2 weeks, and the remaining nodule was removed by Mohs excision [135]. The mechanism of KA induced by imiquimod remains unclear and may be related to the localized abnormal and exuberant immunological response [134].

Squamous Cell Carcinoma

SCC is the second most common malignant skin tumor and is closely associated with sun exposure. The standard treatment for SCC is surgical excision [137]. Recently, topical

imiquimod has gained favorability as a non-surgical option for SCC due to its potential antitumor properties which involve enhancing innate and acquired immunity. However, the occurrence or progression of SCC induced by imiquimod has been reported, although it is rare.

Topical imiquimod treatment for AK and SCC in situ (Bowen disease) has been reported to lead to the development of SCC. Moderate to intense local reactions, such as erythema, desquamation, edema, and itching, were observed in three patients [7, 138, 139]. The primary lesions were completely cleared in all but one patient after imiquimod treatment, indicating the effectiveness of topical imiquimod treatment. However, new tumors subsequently developed on the previously treated lesions 6 weeks to 12 months after commencing treatment with imiquimod. The diagnosis of SCC is not difficult based on clinical manifestations and pathological findings. The prognosis of these reported patients varied. Three patients recovered without recurrence after surgical excision or solid cryosurgery [7, 138], whereas one patient died from SCC progression [140]. Lymph node metastasis, neoplastic parotid involvement, and skull bone invasion were also observed in some patients [138, 140]. Regarding the mechanism, a current hypothesis suggests that imiquimod might alter the tumor microenvironment equilibrium by switching the Th2 immune response to Th1, leading to a change in the immunosurveillance and tumor editing processes, which may be responsible for the development of SCC following imiquimod treatment [140, 141].

Melanoma

In addition to SCC, 5% imiquimod cream has also been used off-label to treat cutaneous metastases of melanoma (MM), and has even been considered the first-line therapy for MM in situ (lentigo maligna) [3, 8, 142, 143]. However, it should be noted that cases of MM arising following topical imiquimod treatment have also been reported. Furthermore, imiquimod is also likely to potentiate the MM development.

A 60-year-old male patient was treated with imiquimod (five consecutive times/week, 6 weeks) due to a biopsy-proven BCC on his mid back. Complete cure of the BCC and a newly emerging pigmented lesion at the application site were observed simultaneously at week 8 after beginning the treatment. The lesion was surgically resected and histologically confirmed to be invasive MM [3]. Dika et al. [143] reported an 89-year-old woman diagnosed with in-transit melanoma metastases who received a combination of diathermocoagulation ablation and topical imiquimod. Although clinical remission was achieved, the disease progressed from IIIC to IV after 3 months, with the patient ultimately dying from complicated paraneoplastic ascites. Given the rarity of these cases and the pleiotropic antitumoral responses of imiquimod, it is difficult to explore the specific mechanism, and the exuberant immunological response induced by imiquimod as well as the influence of imiquimod on immunosurveillance and tumor editing may be involved [3, 143].

Considering that skin tumors, especially more aggressive tumors, have been reported to develop or progress after the topical use of imiquimod against AK, BCC, and SCC in situ, the importance of regular long-term clinical follow-up cannot be overstated.

Others

Moreover, topical imiquimod used in the treatment of genital warts resulted in the complete remission of warts and the occurrence of lichen sclerosus in a 37-year-old man [112]. Barton [144] reported success in treating a patient who had Bowen's disease through the topical application of 5% imiquimod; however, angioedema developed 3 weeks after drug initiation. Stephenson and colleagues [145] reported that a 6-year-old girl for whom imiquimod was used to treat flat warts accidentally applied it to a nearby annular granuloma lesion. The lesion expanded and thickened within 1 month but returned to its previous baseline morphology after the use of imiquimod was stopped. Cavicchini et al. [146] reported that one patient developed morbilliform exanthem on his trunk and arms 22 days after imiquimod therapy for five biopsy-proven superficial BCCs on his shoulders.

CONCLUSION

Due to its mode of action, the topical use of imiquimod can activate immune cells and induce the release of proinflammatory cytokines by binding to TLRs, further promoting the Th1 response and enhancing the activation of cytotoxic T cells, which play an excellent antitumor and antiviral role and have shown strong therapeutic effects [111]. Based on this, imiquimod has expanded the treatment strategies for viral infections of the skin and localized tumors and has allowed patients to undergo convenient self-medication/home treatment. However, the excessive release of cytokines and inappropriate inactivation of the immune system induced by imiquimod may precipitate or exacerbate certain autoimmune diseases and inflammatory dermatoses, e.g., vitiligo, psoriasis, EM, and LP, as the adverse events we mentioned above; therefore, due caution must be taken when using imiquimod, especially in patients with a personal or family history of these diseases.

The diagnosis of imiquimod-induced dermatoses is not straightforward, and these conditions are easily to misdiagnose and miss, which is in part because some patients, especially elderly patients, might use more than one drug during the same period. In addition, even for the same dermatoses induced by imiquimod, the incubation times can be different for different individuals, varying from several days to several months or even years. Unlike the relatively short incubation periods of most drug reactions, the prolonged latent time makes it more challenging to identify the culprit drug. Prompt withdrawal of imiquimod and avoiding re-exposure are critical to recovery. It might be helpful to establish an accurate system to record the medication history and related side effects to trace pathogenic drugs. Interestingly, there have been cases of dermatosis that may have been induced by imiquimod, such as DLE, vitiligo, and KA, that were treated successfully by imiquimod [132, 147]. Therefore, it is important not to mistake these primary diseases for cutaneous reactions secondary to topical imiquimod treatment.

Although imiquimod is only currently approved by the FDA for external genital and perianal warts in children aged 12 years or more [1], it has been used off-label to treat other pediatric dermatoses, including molluscum contagiosum, verruca plana, and verruca vulgaris, which has led to increasing reports of side effects such as psoriasis, pemphigus, and erythema, as we mentioned above [58, 65, 88]. Thus, there are objections to the use of imiquimod for molluscum contagiosum in children due to the potential adverse effects, treatment costs, and limited effect [88]. We suggest that weighing the pros and cons is necessary in the choice of treatment strategy.

Although topical administration of imiquimod is considered well tolerated, dermatologists should be vigilant about the potential side effects. It is important to note that some of these side effects are irreversible and may lead to interruptions of therapy, further reducing patient satisfaction and compliance with the treatment. Additionally, the minority of these side effects are virtually irreversible and could even induce patient death. Although the incidence of these rare cutaneous side effects is currently very low, an increasing number of side effects will inevitably arise due to the off-label usage of imiquimod, which has been expanding, and new routes of topical administration, such as intravaginal suppositories, that have been explored [122]. Thus, clinicians should be aware of these potential risks related to imiquimod, and patients must be adequately informed about such possible adverse reactions, including but not limited to localized or generalized cutaneous conditions, before treatment. Regular follow-up is crucial to detect potential risks during and after treatment.

ACKNOWLEDGEMENTS

Funding. This work was supported by the 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University, which includes the funding of the rapid service fee.

Author Contributions. Xiaoyan Zhang, Yao Xie, and Lin Wang participated equally in drafting, reviewing, and/or revising the manuscript.

Disclosures. Xiaoyan Zhang, Yao Xie, and Lin Wang have no competing interest for the current manuscript.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Available. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Hanna E, Abadi R, Abbas O. Imiquimod in dermatology: an overview. Int J Dermatol. 2016;55(8):831–44. https://doi.org/10.1111/ijd.13235.

2. Miller RL, Gerster JF, Owens ML, Slade HB, Tomai MA. Imiquimod applied topically: a novel immune response modifier and new class of drug. Int J Immunopharmacol. 1999;21(1):1–14. https://doi.org/10.1016/s0192-0561(98)00068-x.

3. Paul SP. Melanoma arising after imiquimod use. Case Rep Med. 2014;2014:267535. https://doi.org/10.1155/2014/267535.

4. Harrison CJ, Jenski L, Voychehovski T, Bernstein DI. Modification of immunological responses and clinical disease during topical R-837 treatment of genital HSV-2 infection. Antiviral Res. 1988;10(4–5):209–23. https://doi.org/10.1016/0166-3542(88)90032-0.

5. Tyring S. Imiquimod applied topically: a novel immune response modifier. Skin Therapy Lett. 2001;6(6):1–4.

6. Telo I, Pescina S, Padula C, Santi P, Nicoli S. Mechanisms of imiquimod skin penetration. Int J Pharm. 2016;511(1):516–23. https://doi.org/10.1016/j.ijpharm.2016.07.043.

7. Fernandez-Vozmediano J, Armario-Hita J. Infiltrative squamous cell carcinoma on the scalp after treatment with 5% imiquimod cream. J Am Acad Dermatol. 2005;52(4):716–7. https://doi.org/10.1016/j.jaad.2004.11.024.

8. Scarfi F, Patrizi A, Veronesi G, Lambertini M, Tartari F, Mussi M, et al. The role of topical imiquimod in melanoma cutaneous metastases: a critical review of the literature. Dermatol Ther. 2020;33(6):e14165. https://doi.org/10.1111/dth.14165.

9. Gerster JF, Lindstrom KJ, Miller RL, Tomai MA, Birmachu W, Bomersine SN, et al. Synthesis and structure–activity-relationships of 1*H*-imidazo[4,5-*c*]quinolines that induce interferon production. J Med Chem. 2005;48(10):3481–91. https://doi.org/10.1021/jm049211v.

10. Cantisani C, Lazic T, Richetta AG, Clerico R, Mattozzi C, Calvieri S. Imiquimod 5% cream use in dermatology, side effects and recent patents. Recent Pat Inflamm Allergy Drug Discov. 2012;6(1):65–9. https://doi.org/10.2174/187221312798889301.

11. Neumann I, Patalay R, Kaushik M, Timlin H, Daniel C. Treatment of periocular lentigo maligna with topical 5% Imiquimod: a review. Eye (Lond). 2022. https://doi.org/10.1038/s41433-022-02165-5.

12. Wenzel J, Uerlich M, Haller O, Bieber T, Tueting T. Enhanced type I interferon signaling and recruitment of chemokine receptor CXCR3-expressing lymphocytes into the skin following treatment with the TLR7-agonist imiquimod. J Cutan Pathol. 2005;32(4):257–62. https://doi.org/10.1111/j.0303-6987.2005.00297.x.

13. Gilliet M, Conrad C, Geiges M, Cozzio A, Thurlimann W, Burg G, et al. Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. Arch Dermatol. 2004;140(12):1490–5. https://doi.org/10.1001/archderm.140.12.1490.

14. Schon MP, Schon M, Klotz KN. The small antitumoral immune response modifier imiquimod interacts with adenosine receptor signaling in a TLR7- and TLR8-independent fashion. J Invest Dermatol. 2006;126(6):1338–47. https://doi.org/10.1038/sj.jid.5700286.

15. Schon MP, Schon M. Immune modulation and apoptosis induction: two sides of the antitumoral activity of imiquimod. Apoptosis. 2004;9(3):291–8. https://doi.org/10.1023/b:appt.0000025805.55340.c3.

16. Deza G, Martin-Ezquerra G, Curto-Barredo L, Villar Garcia J, Pujol RM. Successful treatment of hypertrophic herpes simplex genitalis in HIV-infected patient with topical imiquimod. J Dermatol. 2015;42(12):1176–8. https://doi.org/10.1111/1346-8138.12969.

17. Borella F, Preti M, Vieira-Baptista P, Perez-Lopez FR, Bertero L, Gallio N, et al. Vulvar Paget's disease: outcomes of 51 patients treated with imiquimod cream. Maturitas. 2022;163:23–7. https://doi.org/10.1016/j.maturitas.2022.05.010.

18. Marti-Marti I, Alsina M, Giavedoni P, Fuertes I. Cutaneous leishmaniasis of the face treated with imiquimod 3.75. Enferm Infecc Microbiol Clin (Engl Ed). 2021;39(2):108–9. https://doi.org/10.1016/j.eimc.2020.04.005.

19. Kubicki SL, Park KE, Aung PP, Duvic M. Complete resolution of primary cutaneous anaplastic large cell lymphoma with topical imiquimod. J Drugs Dermatol. 2019;18(5):460–2.

20. Shalabi D, Vadalia N, Nikbakht N. Revisiting imiquimod for treatment of folliculotropic mycosis fungoides: a case report and review of the literature. Dermatol Ther (Heidelb). 2019;9(4):807–14. https://doi.org/10.1007/s13555-019-00317-2.

21. Barr KL, Konia TH, Fung MA. Lupus erythematosus-like imiquimod reaction: a diagnostic pitfall. J Cutan Pathol. 2011;38(4):346–50. https://doi.org/10.1111/j.1600-0560.2010.01592.x.

22. Campagne G. Successful treatment of a high-grade intraepithelial neoplasia with imiquimod, with vulvar pemphigus as a side effect. Eur J Obstet Gynecol Reprod Biol. 2003;109(2):224–7. https://doi.org/10.1016/s0301-2115(02)00482-7.

23. Yanes DA, Kaffenberger JA, Carr DR. Erythema multiforme as a reaction to imiquimod 5% cream. Dermatol Online J. 2017;23(2):18

24. Tkachenko E, Lin JY, Hartman RI. Regional vitiligo induced by imiquimod treatment for in-transit melanoma metastases. JAAD Case Rep. 2019;5(5):427–9. https://doi.org/10.1016/j.jdcr.2019.03.015.

25. Vaccaro M, Barbuzza O, Guarneri B. Erosive pustular dermatosis of the scalp following treatment with topical imiquimod for actinic keratosis. Arch Dermatol. 2009;145(11):1340–1. https://doi.org/10.1001/archdermatol.2009.278.

26. Fanti PA, Dika E, Vaccari S, Miscial C, Varotti C. Generalized psoriasis induced by topical treatment of actinic keratosis with imiquimod. Int J Dermatol. 2006;45(12):1464–5. https://doi.org/10.1111/j.1365-4632.2006.02980.x.

27. Santos-Juanes J, Esteve A, Mas-Vidal A, Coto-Segura P, Salgueiro E, Gomez E, et al. Acute renal failure caused by imiquimod 5% cream in a renal transplant patient: review of the literature on side effects of imiquimod. Dermatology. 2011;222(2):109–12. https://doi.org/10.1159/000323737.

28. Brown T, Zirvi M, Cotsarelis G, Gelfand JM. Vitiligo-like hypopigmentation associated with imiquimod treatment of genital warts. J Am Acad Dermatol. 2005;52(4):715–6. https://doi.org/10.1016/j.jaad.2004.10.861.

29. Long FQ, Zhao LS, Qian YH. Vitiligo or vitiligo-like hypopigmentation associated with imiquimod treatment of condyloma acuminatum: not a casual event. Chin Med J (Engl). 2017;130(4):503–4. https://doi.org/10.4103/0366-6999.199846.

30. Wang HW, Miao F, Shi L, Lu T, Huang Z, Wang XL. Imiquimod-induced localized vitiligo in wife and lichen planus in husband. Chin Med J (Engl). 2013;126(13):2593.

31. Alatabani M, Ghobara Y, Alissa A. Vitiligo-like depigmentation following treatment with imiquimod 5% cream for condylomata acuminata. Case Rep Dermatol. 2021;13(1):36–41. https://doi.org/10.1159/000510736.

32. Stefanaki C, Nicolaidou E, Hadjivassiliou M, Antoniou C, Katsambas A. Imiquimod-induced vitiligo in a patient with genital warts. J Eur Acad Dermatol Venereol. 2006;20(6):755–6. https://doi.org/10.1111/j.1468-3083.2006.01533.x.

33. Kumar B, Narang T. Local and systemic adverse effects to topical imiquimod due to systemic immune stimulation. Sex Transm Infect. 2011;87(5):432. https://doi.org/10.1136/sextrans-2011-050025.

34. Al-Dujaili Z, Hsu S. Imiquimod-induced vitiligo. Dermatol Online J. 2007;13(2):10.

35. Senel E, Seckin D. Imiquimod-induced vitiligo-like depigmentation. Indian J Dermatol Venereol Leprol. 2007;73(6):423. https://doi.org/10.4103/0378-6323.37065.

36. Serra MC, Menicanti C, Pennacchioli E, Tosti G. Vulvar vitiligo-like depigmentation and multiple halos of hypomelanosis at the trunk following treatment with imiquimod 5% cream for vulvar condylomata: casual or related events? An Bras Dermatol. 2014;89(5):806–7. https://doi.org/10.1590/abd1806-4841.20143058.

37. Li W, Xin H, Ge L, Song H, Cao W. Induction of vitiligo after imiquimod treatment of condylomata acuminata. BMC Infect Dis. 2014;14:329. https://doi.org/10.1186/1471-2334-14-329.

38. Garcia-Montero P, Repiso Jimenez JB, Fernandez Morano MT, de Troya MM. Genital vitiligo-like hypopigmentation after treatment with 5% imiquimod. Actas Dermosifiliogr. 2017;108(4):378–80. https://doi.org/10.1016/j.ad.2016.10.007.

39. Gowda S, Tillman DK, Fitzpatrick JE, Gaspari AA, Goldenberg G. Imiquimod-induced vitiligo after treatment of nodular basal cell carcinoma. J Cutan Pathol. 2009;36(8):878–81. https://doi.org/10.1111/j.1600-0560.2008.01134.x.

40. Sriprakash K, Godbolt A. Vitiligo-like depigmentation induced by imiquimod treatment of superficial basal cell carcinoma. Australas J Dermatol. 2009;50(3):211–3. https://doi.org/10.1111/j.1440-0960.2009.00541.x.

41. Burnett CT, Kouba DJ. Imiquimod-induced depigmentation: report of two cases and review of the literature. Dermatol Surg. 2012;38(11):1872–5. https://doi.org/10.1111/j.1524-4725.2012.02512.x.

42. Mendonca CO, Yates VM. Permanent facial hypopigmentation following treatment with imiquimod cream. Clin Exp Dermatol. 2006;31(5):721–2. https://doi.org/10.1111/j.1365-2230.2006.02175.x.

43. Jacob SE, Blyumin M. Vitiligo-like hypopigmentation with poliosis following treatment of superficial basal cell carcinoma with imiquimod. Dermatol Surg. 2008;34(6):844–5. https://doi.org/10.1111/j.1524-4725.2008.34158.x.

44. Edgar N, Pilkington S, Hogan DJ. Imiquimod-induced hypopigmentation following treatment of periungual verruca vulgaris. Cutis. 2018;101(6):466–8.

45. Kwon HH, Cho KH. Induction of vitiligo-like hypopigmentation after imiquimod treatment of extramammary Paget's disease. Ann Dermatol. 2012;24(4):482–4. https://doi.org/10.5021/ad.2012.24.4.482.

46. Kim NH, Lee JB, Yun SJ. Development of vitiligo-like depigmentation after treatment of lentigo maligna melanoma with 5% imiquimod cream. Ann Dermatol. 2018;30(4):454–7. https://doi.org/10.5021/ad.2018.30.4.454.

47. Oiso N, Narita T, Kawada A. Imiquimod-induced vitiligo-like depigmentation over multiple solar keratosis in a patient with vitiligo. Eur J Dermatol. 2017;27(1):77–8. https://doi.org/10.1684/ejd.2016.2891.

48. Mori S, Akasaka T. Imiquimod-induced vitiligo-like hypopigmentation after treatment for radiation keratosis. Clin Exp Dermatol. 2016;41(8):930–2. https://doi.org/10.1111/ced.12921.

49. Yuan J, Ni G, Wang T, Mounsey K, Cavezza S, Pan X, et al. Genital warts treatment: beyond imiquimod. Hum Vaccin Immunother. 2018;14(7):1815–9. https://doi.org/10.1080/21645515.2018.1445947.

50. Mashiah J, Brenner S. Possible mechanisms in the induction of vitiligo-like hypopigmentation by topical imiquimod. Clin Exp Dermatol. 2008;33(1):74–6. https://doi.org/10.1111/j.1365-2230.2007.02520.x.

51. Kim CH, Ahn JH, Kang SU, Hwang HS, Lee MH, Pyun JH, et al. Imiquimod induces apoptosis of human melanocytes. Arch Dermatol Res. 2010;302(4):301–6. https://doi.org/10.1007/s00403-009-1012-0.

52. Conrad C, Di Domizio J, Mylonas A, Belkhodja C, Demaria O, Navarini AA, et al. TNF blockade induces a dysregulated type I interferon response without autoimmunity in paradoxical psoriasis. Nat Commun. 2018;9(1):25. https://doi.org/10.1038/s41467-017-02466-4.

53. Balak DM, Hajdarbegovic E. Drug-induced psoriasis: clinical perspectives. Psoriasis (Auckl). 2017;7:87–94. https://doi.org/10.2147/PTT.S126727.

54. Igari S, Ohtsuka M, Yamamoto T. Imiquimod-induced widespread psoriasiform eruptions. Eur J Dermatol. 2019;29(2):225–7. https://doi.org/10.1684/ejd.2019.3517.

55. Tsutsumi R, Yoshida Y, Yamamoto O. Imiquimod-induced psoriatic erythroderma treated with infliximab. Acta Derm Venereol. 2017;97(2):279–80. https://doi.org/10.2340/00015555-2495.

56. Patel U, Mark NM, Machler BC, Levine VJ. Imiquimod 5% cream induced psoriasis: a case report, summary of the literature and mechanism. Br J Dermatol. 2011;164(3):670–2. https://doi.org/10.1111/j.1365-2133.2010.10124.x.

57. Nakamura K, Arakawa Y, Masuda K, Arita T, Katoh N, Asai J. Exacerbation of psoriatic arthritis due to topical imiquimod therapy. Int J Dermatol. 2022. https://doi.org/10.1111/ijd.16360.

58. Smith WA, Siegel D, Lyon VB, Holland KE. Psoriasiform eruption and oral ulcerations as adverse effects of topical 5% imiquimod treatment in children: a report of four cases. Pediatr Dermatol. 2013;30(6):e157–60. https://doi.org/10.1111/j.1525-1470.2012.01780.x.

59. Rajan N, Langtry JA. Generalized exacerbation of psoriasis associated with imiquimod cream treatment of superficial basal cell carcinomas. Clin Exp Dermatol. 2006;31(1):140–1. https://doi.org/10.1111/j.1365-2230.2005.01938.x.

60. Wu JK, Siller G, Strutton G. Psoriasis induced by topical imiquimod. Australas J Dermatol. 2004;45(1):47–50. https://doi.org/10.1111/j.1440-0960.2004.00030.x.

61. Oyama S, Funasaka Y, Tsuchiya SI, Kawana S, Saeki H. Increased number of mast cells in the dermis in actinic keratosis lesions effectively treated with imiquimod. J Dermatol. 2017;44(8):944–9. https://doi.org/10.1111/1346-8138.13821.

62. Trayes KP, Love G, Studdiford JS. Erythema multiforme: recognition and management. Am Fam Physician. 2019;100(2):82–8.

63. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on erythema multiforme. Clin Rev Allergy Immunol. 2018;54(1):177–84. https://doi.org/10.1007/s12016-017-8667-7.

64. Tedman A, Malla U, Vasanthakumar L, Buzacott K, Banney L. Stevens-Johnson syndrome due to topical imiquimod 5%. Aust J Gen Pract. 2020;49(10):662–4. https://doi.org/10.31128/AJGP-11-19-5145.

65. Chan MYL, Kennedy J, Oakley A. Erythema multiforme triggered by imiquimod 5% cream. Australas J Dermatol. 2017;58(4):e257–8. https://doi.org/10.1111/ajd.12578.

66. Maxfield L, Gaston D, Peck A, Hansen K. Topical imiquimod and subsequent erythema multiforme. J Am Osteopath Assoc. 2019. https://doi.org/10.7556/jaoa.2020.010.

67. Trcko K. Imiquimod-associated erythema multiforme. Acta Dermatovenerol Alp Pannonica Adriat. 2020;29(1):47–9.

68. Ballester I, Guijarro J, Silvestre JF, Niveiro M. Erythema multiforme induced by imiquimod 5% cream. Int J Dermatol. 2014;53(7):e347–8. https://doi.org/10.1111/ijd.12265.

69. Garcia-Arpa M, Rodriguez-Vazquez M, Delgado Portela M, Vera IE. Erythema multiforme due to 5% imiquimod cream. Actas Dermosifiliogr. 2010;101(6):551–2. https://doi.org/10.1016/s1578-2190(10)70842-8.

70. Rubin RL. Evolving and expanding scope of lupus-inducing drugs. Ann Rheum Dis. 2019;78(4):443–5. https://doi.org/10.1136/annrheumdis-2018-214785.

71. Maguiness SM, Farsani TT, Zedek DC, Berger TG. Imiquimod-induced subacute cutaneous lupus erythematosus-like changes. Cutis. 2015;95(6):349–51.

72. Nomura A, Mizuno M, Noto D, Aoyama A, Kuga T, Murayama G, et al. Different spatial and temporal roles of monocytes and monocyte-derived cells in the pathogenesis of an imiquimod induced lupus model. Front Immunol. 2022;13:764557. https://doi.org/10.3389/fimmu.2022.764557.

73. Lafyatis R, Marshak-Rothstein A. Toll-like receptors and innate immune responses in systemic lupus erythematosus. Arthritis Res Ther. 2007;9(6):222. https://doi.org/10.1186/ar2321.

74. Kim WU, Sreih A, Bucala R. Toll-like receptors in systemic lupus erythematosus; prospects for therapeutic intervention. Autoimmun Rev. 2009;8(3):204–8. https://doi.org/10.1016/j.autrev.2008.07.046.

75. Yokogawa M, Takaishi M, Nakajima K, Kamijima R, Fujimoto C, Kataoka S, et al. Epicutaneous application of toll-like receptor 7 agonists leads to systemic autoimmunity in wild-type mice: a new model of systemic lupus erythematosus. Arthritis Rheumatol. 2014;66(3):694–706. https://doi.org/10.1002/art.38298.

76. Giraud S, Leducq S, Kervarrec T, Barbarot S, Laghmari O, Samimi M. Spectrum of imiquimod-induced lupus-like reactions: report of two cases. Dermatol Ther. 2020;33(1):e13148. https://doi.org/10.1111/dth.13148.

77. Gonzalez Fernandez D, Requena Lopez S, Valdes PF. Erythematous lesion on the nose. Actas Dermosifiliogr (Engl Ed). 2018;109(2):173–4. https://doi.org/10.1016/j.ad.2016.07.029.

78. Chan MP, Zimarowski MJ. Lupus erythematosus-like reaction in imiquimod-treated skin: a report of 2 cases. Am J Dermatopathol. 2011;33(5):523–7. https://doi.org/10.1097/DAD.0b013e3181f2bf9e.

79. Wenzel J, Tuting T. An IFN-associated cytotoxic cellular immune response against viral, self-, or tumor antigens is a common pathogenetic feature in "interface dermatitis." J Investig Dermatol. 2008;128(10):2392–402. https://doi.org/10.1038/jid.2008.96.

80. Jimenez-Gallo D, Brandao BJF, Arjona-Aguilera C, Baez-Perea JM, Linares-Barrios M. Imiquimod-induced cutaneous lupus erythematosus with antinuclear antibodies showing a homogenous pattern. Clin Exp Dermatol. 2017;42(7):795–7. https://doi.org/10.1111/ced.13174.

81. Safadi MG, Hassan S, Patel V, Viglione M, Zahner SL. Imiquimod-induced hypertrophic lupus erythematosus-like reaction. Dermatol Online J. 2022. https://doi.org/10.5070/d328458526.

82. Lim YL, Bohelay G, Hanakawa S, Musette P, Janela B. Autoimmune pemphigus: latest advances and emerging therapies. Front Mol Biosci. 2021;8:808536. https://doi.org/10.3389/fmolb.2021.808536.

83. Moro F, Ciccone D, Fania L, Mariotti F, Salemme A, Rahimi S, et al. Case report: a rare case of imiquimod-induced atypical pemphigus vulgaris. Front Med (Lausanne). 2022;9:1054544. https://doi.org/10.3389/fmed.2022.1054544.

84. Tavakolpour S. Pemphigus trigger factors: special focus on pemphigus vulgaris and pemphigus foliaceus. Arch Dermatol Res. 2018;310(2):95–106. https://doi.org/10.1007/s00403-017-1790-8.

85. Ghaedi F, Etesami I, Aryanian Z, Kalantari Y, Goodarzi A, Teymourpour A, et al. Drug-induced pemphigus: a systematic review of 170 patients. Int Immunopharmacol. 2021;92:107299. https://doi.org/10.1016/j.intimp.2020.107299.

86. Fleischmann M, Celerier P, Bernard P, Litoux P, Dreno B. Long-term interferon-alpha therapy induces autoantibodies against epidermis. Dermatology. 1996;192(1):50–5. https://doi.org/10.1159/000246315.

87. Sebaratnam DF, Martin LK, Rubin AI, Tran K, Pas HH, Marr PJ, et al. Reversible relapse of pemphigus foliaceus triggered by topical imiquimod suggests that Toll-like receptor 7 inhibitors may be useful treatments for pemphigus. Clin Exp Dermatol. 2011;36(1):91–3. https://doi.org/10.1111/j.1365-2230.2010.03918.x.

88. Zhong CS, Hasbun MT, Jones KM, Schmidt BAR, Hussain SH. Pemphigus-like eruption as a complication of molluscum contagiosum treatment with imiquimod in a 5-year-old girl. Pediatr Dermatol. 2020;37(2):379–80. https://doi.org/10.1111/pde.14115.

89. Lin R, Ladd DJ Jr, Powell DJ, Way BV. Localized pemphigus foliaceus induced by topical imiquimod treatment. Arch Dermatol. 2004;140(7):889–90. https://doi.org/10.1001/archderm.140.7.889.

90. Shiraishi K, Sayama K. Pemphigus foliaceus induced by topical imiquimod treatment. Int J Dermatol. 2018;57(12):e155–7. https://doi.org/10.1111/ijd.14204.

91. Lo Schiavo A, Sangiuliano S, Puca RV, Brunetti G, Ruocco E, Cozzi R. Contact pemphigus: a side-effect of imiquimod therapy. Int J Dermatol. 2008;47(7):765–7. https://doi.org/10.1111/j.1365-4632.2008.03533.x.

92. Bauza A, Del Pozo LJ, Saus C, Martin A. Pemphigus-like lesions induced by imiquimod. Clin Exp Dermatol. 2009;34(5):e60–2. https://doi.org/10.1111/j.1365-2230.2008.03181.x.

93. Mashiah J, Brenner S. Possible mechanisms in the induction of pemphigus foliaceus by topical imiquimod treatment. Arch Dermatol. 2005;141(7):908–9. https://doi.org/10.1001/archderm.141.7.908. (**author reply 9**).

94. Di Lernia V, Casanova DM, Goldust M, Ricci C. Pemphigus vulgaris and bullous pemphigoid: update on diagnosis and treatment. Dermatol Pract Concept. 2020;10(3):e2020050. https://doi.org/10.5826/dpc.1003a50.

95. Mufti A, Lytvyn Y, Maliyar K, Sachdeva M, Yeung J. Drugs associated with development of pityriasis rubra pilaris: a systematic review. J Am Acad Dermatol. 2021;84(4):1071–81. https://doi.org/10.1016/j.jaad.2020.07.052.

96. Yang FC, Jessup C, Dahiya M, Reynolds R. Pityriasis rubra pilaris exacerbation with topical use of imiquimod. Int J Dermatol. 2008;47(10):1076–8. https://doi.org/10.1111/j.1365-4632.2008.03729.x.

97. Leite OG, Tagliolatto S, Souza EM, Cintra ML. Acantholytic pityriasis rubra pilaris associated with topical use of imiquimod 5%: case report and literature review. An Bras Dermatol. 2020;95(1):63–6. https://doi.org/10.1016/j.abd.2019.01.009.

98. Gomez-Moyano E, Crespo-Erchiga A, Vera Casano A, Sanz TA. Pityriasis rubra pilaris with focal acantholytic dyskeratosis during treatment with imiquimod 5% cream. Actas Dermosifiliogr. 2010;101(10):898–900.

99. Atanaskova Mesinkovska N, Dawes D, Sood A, Bergfeld W. Acantholytic pityriasis rubra pilaris associated with imiquimod 3.75% application. Case Rep Dermatol Med. 2011;2011:412684. https://doi.org/10.1155/2011/412684.

100. Magro CM, Crowson AN. The clinical and histomorphological features of pityriasis rubra pilaris. A comparative analysis with psoriasis. J Cutan Pathol. 1997;24(7):416–24. https://doi.org/10.1111/j.1600-0560.1997.tb00816.x.

101. Karanfilian KM, Wassef C. Erosive pustular dermatosis of the scalp: causes and treatments. Int J Dermatol. 2021;60(1):25–32. https://doi.org/10.1111/ijd.14955.

102. Giuffrida R, Borgia F, Cannavo SP. Two cases of erosive pustular dermatosis of the scalp occurring after topical 3.75% imiquimod for actinic keratoses. Dermatol Ther. 2019;32(1):e12770. https://doi.org/10.1111/dth.12770.

103. Piccolo V, Russo T, Bianco S, Ronchi A, Alfano R, Argenziano G. Erosive pustular dermatosis of the scalp: why do we miss It? Dermatology. 2019;235(5):390–5. https://doi.org/10.1159/000500909.

104. Corradin MT, Forcione M, Giulioni E, Fiorentino R, Ferrazzi A, Alaibac M. Erosive pustular dermatosis of the scalp induced by imiquimod. Case Rep Dermatol Med. 2012;2012:828749. https://doi.org/10.1155/2012/828749.

105. Broussard KC, Berger TG, Rosenblum M, Murase JE. Erosive pustular dermatosis of the scalp: a review with a focus on dapsone therapy. J Am Acad Dermatol. 2012;66(4):680–6. https://doi.org/10.1016/j.jaad.2011.10.011.

106. Van Exel CE, English JC 3rd. Erosive pustular dermatosis of the scalp and nonscalp. J Am Acad Dermatol. 2007;57(2 Suppl):S11–4. https://doi.org/10.1016/j.jaad.2006.07.009.

107. Rongioletti F, Chinazzo C, Javor S. Erosive pustular dermatosis of the scalp induced by ingenol mebutate. J Eur Acad Dermatol Venereol. 2016;30(11):e110–1. https://doi.org/10.1111/jdv.13350.

108. Vaccaro M, Borgia F, Gasco L, Cannavo SP. Erosive pustular dermatosis of the scalp following topical ingenol mebutate for actinic keratoses. Dermatol Ther. 2017. https://doi.org/10.1111/dth.12521.

109. Vollono L, Bianchi L, Mazzilli S, Orlandi A, Bielli A, Campione E. Drug-induced lichen planus pigmentosus: Do supportive and complementary drugs count? Dermatol Ther. 2019;32(3):e12871. https://doi.org/10.1111/dth.12871.

110. Suryana K. Lichenoid reaction caused by antihistamines and corticosteroids. J Asthma Allergy. 2020;13:205–11. https://doi.org/10.2147/JAA.S251046.

111. Brown RS, Farquharson AA. A topical imiquimod-induced oral mucosal lichenoid reaction: a case report. J Am Dent Assoc. 2014;145(11):1141–5. https://doi.org/10.14219/jada.2014.88.

112. O'Mahony C, Yesudian PD, Stanley M. Imiquimod use in the genital area and development of lichen sclerosus and lichen planus. Int J STD AIDS. 2010;21(3):219–21. https://doi.org/10.1258/ijsa.2009.009154.

113. Zhao L, Li K, Long FQ. Development of lichen planus associated with topical imiquimod therapy. Dermatol Ther. 2020;33(3):e13367. https://doi.org/10.1111/dth.13367.

114. Furuoka K, Fukumoto T, Nagai H, Nishigori C. Topical imiquimod-induced lichenoid drug reaction successfully treated with tacrolimus ointment. Dermatol Ther. 2020;33(6):e14480. https://doi.org/10.1111/dth.14480.

115. Drummond A, Pichler J, Argenziano G, Zalaudek I, Longo C, Lallas A, et al. Lichen planopilaris after imiquimod 5% cream for multiple BCC in basal cell naevus syndrome. Australas J Dermatol. 2015;56(4):e105–7. https://doi.org/10.1111/ajd.12151.

116. Domingues E, Chaney KC, Scharf MJ, Wiss K. Imiquimod reactivation of lichen planus. Cutis. 2012;89(6):276–7, 83.

117. Forouzan P, Riahi RR, Cohen PR. Atorvastatin-induced lichenoid drug eruption: a case report and review of statin-associated cutaneous adverse events. Cureus. 2020;12(3):e7155. https://doi.org/10.7759/cureus.7155.

118. Schneider MR, Schmidt-Ullrich R, Paus R. The hair follicle as a dynamic miniorgan. Curr Biol. 2009;19(3):R132–42. https://doi.org/10.1016/j.cub.2008.12.005.

119. Choi BY. Targeting Wnt/beta-catenin pathway for developing therapies for hair loss. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21144915.

120. Kalandarishvili M, Kolbe EW, Winde G, Kaspari M. Chemical gastroenterocolitis after dental root canal therapy with camphorated and mentholated chlorophenol. Case Rep Gastrointest Med. 2021;2021:9918830. https://doi.org/10.1155/2021/9918830.

121. Guo K, Wang L, Zhong Y, Gao S, Jing R, Ye J, et al. Cucurbitacin promotes hair growth in mice by inhibiting the expression of fibroblast growth factor 18. Ann Transl Med. 2022;10(20):1104. https://doi.org/10.21037/atm-22-4423.

122. Borst C, Grimm C, Tanew A, Radakovic S. Imiquimod-induced effluvium after intravaginal

application for treatment of cervical intraepithelial neoplasia. JAAD Case Rep. 2019;5(7):602–4. https://doi.org/10.1016/j.jdcr.2019.04.015.

123. Conde J, Davis K, Ntuen E, Balmer N, Jones D, McMichael A. A case of imiquimod-induced alopecia. J Dermatol Treat. 2010;21(2):122–4. https://doi.org/10.1080/09546630902991484.

124. Patel M, Harrison S, Sinclair R. Drugs and hair loss. Dermatol Clin. 2013;31(1):67–73. https://doi.org/10.1016/j.det.2012.08.002.

125. Amberg N, Holcmann M, Stulnig G, Sibilia M. Effects of imiquimod on hair follicle stem cells and hair cycle progression. J Investig Dermatol. 2016;136(11):2140–9. https://doi.org/10.1016/j.jid.2016.06.613.

126. Letada PR, Sparling JD, Norwood C. Imiquimod in the treatment of alopecia universalis. Cutis. 2007;79(2):138–40.

127. Diluvio L, Campione E, Paterno EJ, Orlandi A, Terrinoni A, Chimenti S. Peculiar clinical and dermoscopic remission pattern following imiquimod therapy of basal cell carcinoma in seborrhoeic areas of the face. J Dermatol Treat. 2009;20(2):124–9. https://doi.org/10.1080/09546630802441226.

128. Kurokawa I, Umeda K, Nishimura K, Yamanaka KI, Hakamada A, Isoda KI, et al. Filaggrin expression and the pathogenesis of epidermal cysts. Br J Dermatol. 2007;157(2):415–6. https://doi.org/10.1111/j.1365-2133.2007.08047.x.

129. Dillies AS, Gras-Champel V, Fraitag-Spinner S, Al Saif F, Carmi E. Eruptive epidermoid cysts during topical imiquimod treatment. Ann Dermatol Venereol. 2017;144(3):212–5. https://doi.org/10.1016/j.annder.2016.09.042.

130. Marty CL, Randle HW, Walsh JS. Eruptive epidermoid cysts resulting from treatment with imiquimod. Dermatol Surg. 2005;31(7 Pt 1):780–2. https://doi.org/10.1097/00042728-200507000-00011. (**discussion 2-3**).

131. Nasca MR, De Pasquale R, Micali G. Multiple and clustered eruptive epidermoid cysts following treatment with topical imiquimod. Dermatology. 2007;215(4):352–3. https://doi.org/10.1159/000107630.

132. Lee JW, Cho KH, Choi CW, Jo SJ. Therapeutic efficacy of topical imiquimod cream on keratoacanthoma: a retrospective single-center study. J Am Acad Dermatol. 2022;87(3):671–4. https://doi.org/10.1016/j.jaad.2021.08.037.

133. Pini AM, Koch S, Scharer L, French LE, Lauchli S, Hofbauer GF. Eruptive keratoacanthoma following topical imiquimod for in situ squamous cell carcinoma of the skin in a renal transplant recipient. J Am Acad Dermatol. 2008;59(5 Suppl):S116–7. https://doi.org/10.1016/j.jaad.2008.06.018.

134. Campalani E, Holden CA. Keratoacanthoma associated with the use of topical imiquimod. Clin Exp Dermatol. 2013;38(5):555–6. https://doi.org/10.1111/j.1365-2230.2012.04476.x.

135. D'Addario S, Carrington PR. Multiple keratoacanthomas as an untoward response to imiquimod therapy for actinic keratoses. Acta Derm Venereol. 2006;86(4):366–7. https://doi.org/10.2340/00015555-0109.

136. Dessoukey MW, Omar MF, Abdel-Dayem H. Eruptive keratoacanthomas associated with immunosuppressive therapy in a patient with systemic lupus erythematosus. J Am Acad Dermatol. 1997;37(3 Pt 1):478–80. https://doi.org/10.1016/s0190-9622(97)70150-6.

137. Han SN, Feng SJ, Ai DF. Clinical treatment study of secondary multiple squamous cell carcinoma with psoriasis vulgaris. J Oncol. 2022;2022:9529681. https://doi.org/10.1155/2022/9529681.

138. Goh MS. Invasive squamous cell carcinoma after treatment of carcinoma in situ with 5% imiquimod cream. Australas J Dermatol. 2006;47(3):186–8. https://doi.org/10.1111/j.1440-0960.2006.00269.x.

139. Singh S, Bunker CB. Squamous cell carcinoma on the scalp following treatment with 5% imiquimod cream. Clin Exp Dermatol. 2007;32(5):594–5. https://doi.org/10.1111/j.1365-2230.2007.02496.x.

140. Dika E, Fanti PA, Lambertini M, Scarfi F, Ravaioli GM, Veronesi G, et al. Cutaneous squamous cell carcinoma progression during imiquimod treatment. J Am Acad Dermatol. 2018;79(1):e11–2. https://doi.org/10.1016/j.jaad.2018.02.079.

141. Schosserer M, Grillari J, Breitenbach M. The dual role of cellular senescence in developing tumors and their response to cancer therapy. Front Oncol. 2017;7:278. https://doi.org/10.3389/fonc.2017.00278.

142. Smyth EC, Flavin M, Pulitzer MP, Gardner GJ, Costantino PD, Chi DS, et al. Treatment of locally recurrent mucosal melanoma with topical imiquimod. J Clin Oncol. 2011;29(33):e809–11. https://doi.org/10.1200/JCO.2011.36.8829.

143. Dika E, Ravaioli GM, Melotti B, Patrizi A, Veronesi G, Lambertini M, et al. In transit melanoma and imiquimod: A case of disease progression. Dermatol Ther. 2020;33(4):e13512. https://doi.org/10.1111/dth.13512.

144. Barton JC. Angioedema associated with imiquimod. J Am Acad Dermatol. 2004;51(3):477–8. https://doi.org/10.1016/j.jaad.2004.01.037.

145. Stephenson S, Nedorost S. Granuloma annulare: dramatically altered appearance after application of 5% imiquimod cream. Pediatr Dermatol. 2008;25(1):138–9. https://doi.org/10.1111/j.1525-1470.2007.00612.x.

146. Cavicchini S, Vezzoli P, Muratori S, Gianotti R. Morbilliform exanthem induced by imiquimod in a patient with drug-related immunosuppression. Clin Exp Dermatol. 2009;34(4):526–7. https://doi.org/10.1111/j.1365-2230.2008.02971.x.

147. Bong AB, Gollnick H, Schon MP. Treatment of vitiligo with topical imiquimod. J Eur Acad Dermatol Venereol. 2004;18(6):741–2. https://doi.org/10.1111/j.1468-3083.2004.01047.x.