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Successful Treatment of Generalized Discoid Lupus Erythematosus with Imiquimod Cream 5%: A Case Report and Review of the Literature

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SUMMARY Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus. It tends to heal with scarring, hair loss, and pigmentary changes if treatment is not initiated in the early phase of the disease. Classic DLE lesions are initially red-purple macules, papules, or small plaques that rapidly acquire a hyperkeratotic appearance. Only a minority of patients with DLE progress to develop systemic lupus erythematosus (SLE). A small percentage of patients with SLE have concomitant DLE. However, generalized DLE is more frequently associated with systemic involvement than classic DLE. The diagnosis of DLE is usually based on clinical features, although in some cases histopathological examination may be required to confirm the diagnosis. Standard therapy for cutaneous lupus erythematosus includes broad-spectrum sunscreens, topical and intralesional glucocorticoids, and antimalarial agents. A 63-year-old man presented with erythematous scaly patches that he had on the face for approximately eight months. Although the face was the main affected site, lesions were also noted on the scalp, neck, chest, shoulder, upper arms, and trunk. Histopathological examination verified the diagnosis of DLE. Laboratory examination and consultation with other departments did not reveal any systemic involvement. Imiquimod cream 5% was applied three times a week, every other week. After 24 applications over a period of two months, an almost complete recovery was achieved. Topical imiquimod may be an alternative treatment for generalized DLE.

KEY WORDS: discoid lupus erythematosus; generalized; imiquimod

INTRODUCTION

Discoid lupus erythematosus (DLE) is a chronic dermatosis characterised by clearly demarcated erythematous patches or plaques that are especially likely to occur on sun-exposed areas. DLE is probably more likely to occur in individuals who are genetically inclined, although definitive genetic risk factors have not yet been identified. The condition generally becomes evident after exposure to ultraviolet (UV) light, but trauma, mental stress, and exposure to cold may also act as triggers (1,2). Although the pathophysiology of DLE is not well known, it was claimed that a triggering factor such as UV light or stress can activate a heat shock protein in keratinocytes. This protein might play a key role in T-cell mediated epidermal cell cytotoxicity (3,4). Recent publications emphasise the role of the toll-like receptors in the pathogenesis of DLE (5-7).

DLE accounts for 55-85% of cases of cutaneous lupus erythematosus (CLE) (8, 9). Lesions may clinically appear as verrucous, hypertrophic, or telangiectatic lesions. Facial lesions expand and join together, leading to a butterfly-shaped rash in the malar region.

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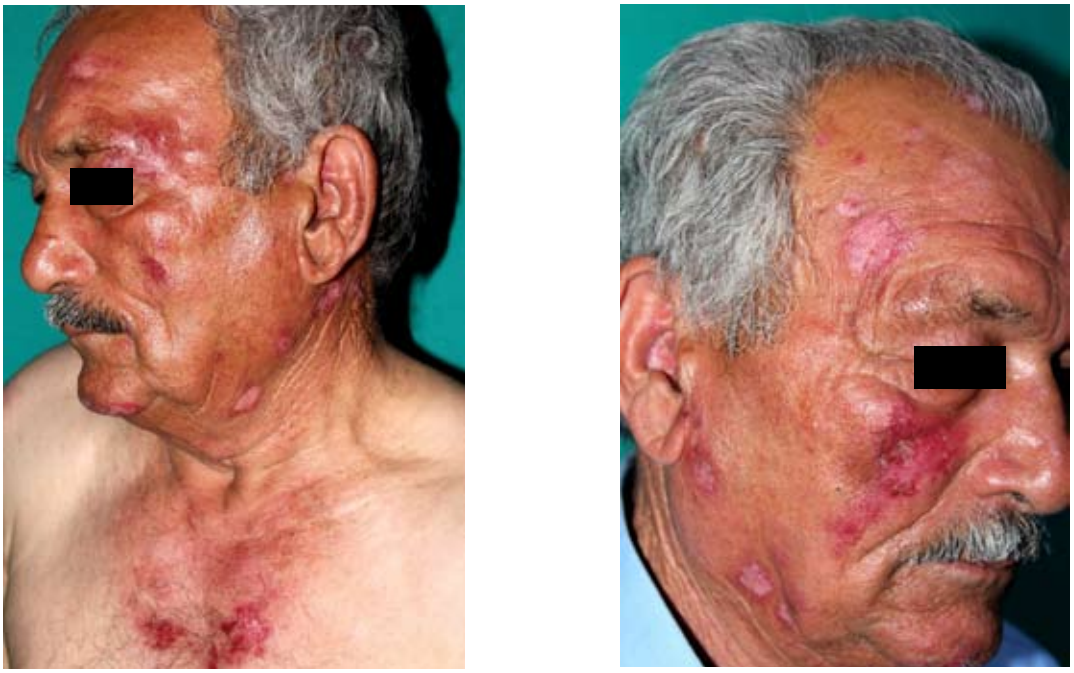

Figure 1, 2. Erythematous and clearly demarcated plaques on the face, neck and chest

This rash is the characteristic skin lesion associated with DLE(1). Over time, hyperpigmentation may develop around the discoid lesions. Plaques and a poikilodermic appearance also develop as a result of atrophic scarring and telangiectasies (8). Several DLE lesions may be found on the head and neck in patients in the localized form of the disease. However, disseminated or generalised DLE is associated with lesions that are widely distributed on the body with or without head and neck involvement (10). Hematological and serological abnormalities are commonly associated with the disseminated form of the disease, which is also associated with a higher risk a of systemic involvement and is more difficult to treat than the localized form (1).

It is necessary to treat DLE in order to improve the patient's appearance, to control existing lesions, to make scarring minimal, and to prevent the development of more lesions. However, therapy continues to be a serious problem for clinicians because the disease tends to reoccur.

Standard therapy for CLE includes broad-spectrum sunscreens, topical, intralesional and/or systemic glucocorticoids, antimalarial agents such as hydroxychloroquine, chloroquine and quinacrine, retinoids, and dapsone (11). In this paper we report on the successful treatment of a 63-year-old man with generalized DLE with topical imiquimod.

CASE REPORT

A 63-year-old man came to our clinic with generalized, erythematous, and clearly demarcated plaques on his face, neck, scalp, shoulder, chest, and upper extremities (Figure 1, 2). The lesions had developed on his face about eight months earlier and then spread accross the entire face and to other areas of his body. The patient's personal and family history was unremarkable. He denied any personal or family history of photosensitivity or any connective-tissue disease. The systemic physical examination did not reveal any pathological findings.

Histopathological examination of the lesions revealed superficial hyperkeratosis with follicular plugging covered by an atrophic epidermis, epidermal dyskeratotic cells, vacuolar degeneration of the basal layer, periadnexal, interstitial and perivascular lymphocytic infiltrates, erythrocyte extravasation, edema, and vasodilation in the dermis (Figure 3). A diagnosis of generalized DLE was made based on the clinical, histopathological, serological and immunological findings. Laboratory evaluations were in the normal range, including a red blood cell count, hemoglobin, hematocrit, erythrocyte sedimentation rate, serum biochemistry, and urinalysis. Serological and immunological parameters failed to uncover any pathology. Anti-double-stranded DNA (dsDNA), SS-A, SS-B, Smith and ribonucleoprotein antibodies were negative. Immunoglobulins (IgG, IgM, IgA) and complements (C3, C4) were within normal limits. A rapid plasma reagin test was non-reactive. Pulmonary X-ray and abdominopelvic ultrasonography were normal, and no systemic involvement was detected.

The patient did not consent to systemic administration of corticosteroids, and his lesions continued

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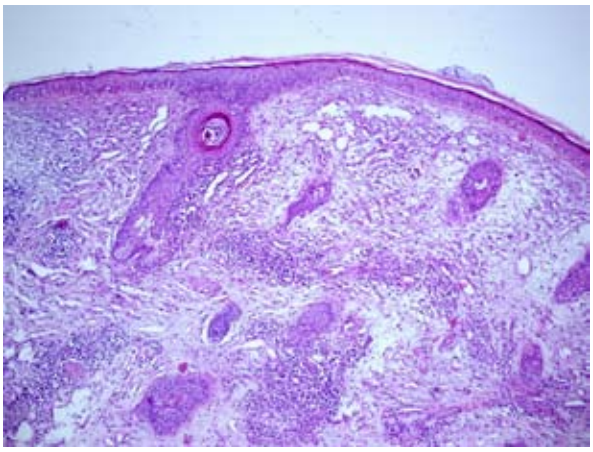

Figure 3. Superficial hyperkeratosis with follicular plugging covered by an atrophic epidermis, epidermal dyskeratotic cells, vacuolar degeneration of the basal layer, superficial and deep perivascular lymphocytic infiltration [hematoxylin and eosin stain (H&E); original magnification X100]

to be active after one month of topical steroid therapy. Therefore, we initiated treatment with topical imiquimod cream 5%, applied three times a week. After two weeks of treatment, erythema and crusting developed on the lesions. Treatment was interrupted for a few days to allow the crusts to heal, and then imiquimod cream was applied for a total of eight weeks. With the topical imiquimod therapy, the lesions gradually regressed and healed significantly after two months. No adverse effects were seen except for local inflammatory reactions and a thin crust formation at the site of treatment and the adjacent skin. At the end of the treatment, the patient had been clinically cured of the disease (Figure 4 and 5). By the time of his one year follow-up, there had been no recurrence and no new lesions had developed.

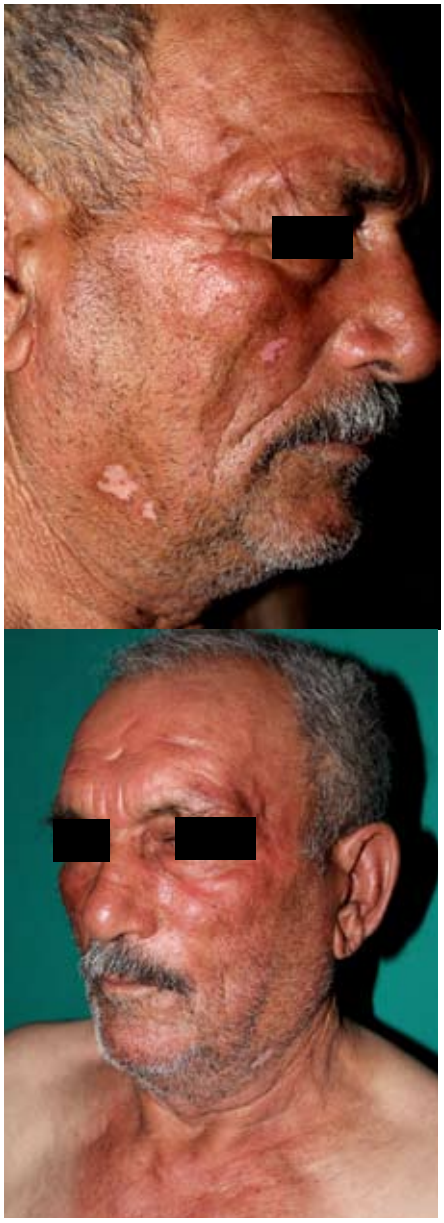

Figure 4, 5. Appearance of the lesions on the face after imiquimod therapy (after12 weeks)

DISCUSSION

DLE treatment aims to control the number of lesions, to minimize scarring, and to prevent the occurrence of new lesions. Standard medical therapy consists of topical or intralesional corticosteroids and antimalarial medications, and broad-spectrum sunscreens are recommended for all patients. Antimalarial agents such as hydroxychloroquine, chloroquine, and quinacrine are indicated when topical or intralesional therapy fails to control the skin disease (2,4) Alternative therapeutic options include topical or systemic retinoids, thalidomide, dapsone, clofazimine, auranofin, gold, sulfasalazine, and immunosuppressive agents such as methotrexate and mycophenolate mofetil (12). Cryotherapy and laser therapy have been reported as therapeutic alternatives for DLE in literature (13,14).

Topical calcineurin inhibitors have recently been successfully used in patients with SLE with skin lesions, but these inhibitors have a limited ability to penetrate discoid lesions. Gerdsen *et al*. reported that they successfully treated a case with DLE of the scalp through the use of imiquimod cream 5% (15). In 2006, successful treatment with imiquimod therapy was reported by Gul *et al*. in patients with generalized DLE where lesions involved the face in particular (16).

Emertcan *et al*. reported on the treatment of a case where microinvasive squamous cell carcinoma (SCC)

developed on the DLE lesions on the lip and around the ears. The patient was treated for five days a week with topical imiquimod 5% and achieved complete healing within two weeks (17).

We found only one case of generalized DLE in the literature that was successfully treated with topical imiquimod. In 2006, Gul *et al*. reported on therapy that included topical imiquimod once a day, three times a week, for a patient with DLE lesions that were located mainly on the face. The lesions totally cleared after 20 applications and, except for local irritation, no serious side effects were noted (16). Our case represents the second time that topical imiquimod cream was used successfully in the treatment of generalized DLE.

Imiquimod modifies the immune response and has antitumor, antiviral, and immunoregulatory properties. Imiquimod acts on both innate and adaptive immune responses. It stimulates production of pro-inflammatory cytokines such as IL-2, IL-12, IL-18, IFN-α, and IFN-γ by activating the toll-like receptor 7 and the nuclear factor kappa B signaling pathway (18). Imiquimod has also been shown to increase T-helper type 1 (Th1) immune responses and to decrease T-helper type 2 (Th2) immune responses. In addition, it activates antigen presentation to T lymphocytes by Langerhans cells and induces apoptosis of the tumor cells through caspase activation. The Food and Drug Administration has approved imiquimod for the treatment of genital warts, actinic keratoses of the head and neck, and superficial basal cell carcinoma. DLE has been reported as one of the off-label indications for imiquimod (19).

Topical imiquimod therapy may cause several side effects, ranging from mild local reactions to serious systemic side effects. Most common local reactions are erythema, scabbing, erosion, induration, edema, and ulceration. Less common systemic side effects are flu-like symptoms, headache, back pain, muscle aches, tiredness, fatigue, swollen lymph nodes, nausea, diarrhea, infections, postural hypotension, and changes in skin color (20).

Burnett *et al.* reported on the development of autoimmune retinitis with subacute cutaneous lupus erythematosus (SCLE) in a 56-year-old female patient who was treated with 5% imiquimod for actinic keratosis. Authors suggested IFN-alpha, which plays an important role in the pathogenesis of SCLE, may be associated with this condition (21). Development of lupus erythematosus-like reactions in the treated region was reported by Chan *et al.* in two different patients (20). These cases indicate diverse imiquimod reaction patterns.

How imiquimod acts in treating DLE is uncertain. Its effect may be associated with the increased levels of IFN-alfa. In the literature there are several reports of DLE and SCLE cases that were treated with IFN alfa 2a (22). Similarly, Martinez *et al*. reported on the treatment of two DLE patients with intralesional IFN-alpha 2b (23). The authors suggested that IFN-alfa anti-inflammatory effects are based on the down-regulation of lymphokin production. Mori *et al*. also reported that expression of functionally meaningful molecules from Langerhans cells suggests the impairment of

Table 1. Cases of DLE treated successfully with imiquimod in the literature

Age	Sex	Location	Simultaneous lesion	History	Previous treatment	Duration of treatment	Side effect	Response	Reference
56	female	scalp	None	6 year	topical corticosteroids, systemic corticosteroids, hydroxychloroquine, Methotrexate Azathioprine, Mycophenolate mofetil, Dapsone	once daily in 2 cycles/3 week	erythema	Complete healing	(15)
44	male	generalized	None	1 year	Topical steroid	3 times a week /20 application (7 week)	local irritation and crusting	Complete healing	(16)
46	female	Face (lip, around ear)	Microinvasive SCC	9 month	None	Five days per week/ Two week	minimal burning and irritation	Complete healing	(17)
63	male	generalized	None	8 month	Topical steroid	three times a week/ eight weeks	inflammatory reactions, thin crust formation	Complete healing	Current case

their immunologic efficiency. The effect of imiquimod on DLE may be associated with its modifying effect on Langerhans cells. However, extended pharmacodynamic studies are needed in order to explain imiquimod's effects on DLE.

CONCLUSION

There are several cases of DLE treated successfully with imiquimod to be found in the literature. Imiquimod may be a therapeutic option for refractory cases in which standard therapy modalities are ineffective or contrindicated. More controlled clinical trials are needed to draw any further conclusions.

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