Review paper

Keratosis follicularis (Darier disease) – clinical characteristics and treatment – a review and update

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Abstract

Darier disease is one of the most common genodermatoses. Although Darier disease was described in 1886, targeted therapies remain unknown. Current literature lacks specific guidelines for treatment of Darier disease. Treatment remains symptomatic and may be challenging for dermatologists. The aim of this article is to present clinical characteristics and treatment options. In a mild form of the disease with a small number of skin lesions, the symptoms can be reduced by the use of topical medications. Oral retinoids, alternatively doxycycline, seem to be beneficial in extensive and persistent lesions unresponsive to local treatment. In limited, hypertrophic forms, surgical methods, laser therapy and photodynamic therapy could be used.

Key words: keratosis follicularis, Darier disease.

Keratosis follicularis (Darier disease, Darier-White disease) is an autosomal dominant genodermatosis, therefore family history is of great importance in its diagnosis. The disease was first described in 1886 by Prince Marrow, then in 1889 independently by Darier and White. The disease occurs in a population with a frequency of 1 in 30,000–100,000, in all ethnic groups, and it is equally common in both genders [1, 2].

Darier disease is connected with a mutation in the ATP2A2 gene, encoding sarco/endoplasmic reticulum ATPase type 2 (SERCA2) [3]. The product of this gene is responsible for the transport of calcium in the endoplasmic reticulum of epidermal cells, and its malfunction causes aberrant epidermal keratinization and abnormal cell adhesion. As Darier disease is characterized by hyperkeratotic papules in seborrheic regions it can be easily misdiagnosed by general practitioners resulting in a delay in diagnosis and appropriate treatment. In addition, dermatologists do not have any evidence-based guidelines for the treatment of Darier disease. Therefore, the need of review and an update of therapeutic options may be handy for dermatologists.

A literature search was conducted in electronic databases using the following key words: 'Darier disease', 'Darier-White disease', 'keratosis follicularis', 'Darier disease & treatment', 'Darier disease & laser treatment', 'Darier-White disease & treatment', 'Darier-White disease & laser treatment', 'keratosis follicularis & treatment', and 'keratosis follicularis & laser treatment'. Papers containing treatment procedures of Darier disease were collected through PubMed, Scopus and national databases from 1992 to 2021.

The first clinical symptoms of Darier disease usually appear in adolescence or early adulthood and may be associated with pruritus. Different factors are thought to exacerbate keratosis follicularis. Some of them include exposure to ultraviolet radiation, mechanical injuries, surgery procedures, humidity, heat, stress, menstruation, pregnancy and childbirth.

Primary lesions are small, strongly corneous red-brown papules covered with a grey keratin plug, located mainly in the seborrheic areas: the forehead, nasolabial folds, neck, scalp, chest, back and flexural regions: armpits, groins and submammary skin. Those lesions are the most bothersome for patients because of the secondary superinfections and malodour. Over time, the eruptions spread creating larger areas clinically presented as dirty warty plaques with the formation of oily scabs.

Hand involvement is common. Punctate keratosis, palmar pits or haemorrhagic macules are visible. On the

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dorsal surfaces of hands and feet, the so-called acrokeratosis verruciformis-like lesions can be found in nearly 50% of patients.

Nail changes are helpful for diagnosis. They include red and white longitudinal bands, nail ridges, subungual hyperkeratosis and V-shaped defects in the free margin of the nail. Rarely, complete nail dystrophy occurs.

On the mucous membranes, the lesions appear as whitish, clustered papules with central depression, described as the image of "cobblestones". Within the oral cavity, lesions are usually located on the cheeks and the palate.

Dyskeratosis follicularis occurs in two forms, which differ in their genotype and clinical picture. In the first type (segmental, linear), lesions are located unilaterally and are found, like epidermal nevi, along the Blaschko's lines. In the second type, which occurs in almost 90% of patients, lesions are diffuse and occur on both sides. Other subtypes include vesiculobullous type, cornifying type, an acral haemorrhagic form, and comedonal Darier disease.

Skin biopsy should be performed to confirm the diagnosis.

It should be emphasized that apart from skin lesions, patients with Darier disease often suffer from neuropsychiatric disorders. Mental retardation, depression, bipolar disorder, suicidal thoughts, psychoses and epilepsy are significantly more common in the group of patients with Darier disease. In addition, ophthalmic disorders may appear. They include recurrent herpes keratitis, minor ulcerations of the corneal epithelium or conjunctival keratosis.

Due to the location, similarity of clinical and microscopic features, the disease should be differentiated from seborrheic dermatitis, acanthosis nigricans, transient acantholytic dermatosis (Grover disease), familial benign pemphigus (Hailey-Hailey disease) and pemphigus vegetans (Table 1). In seborrheic dermatitis, erythema covered with white to yellowish oily scales in the sebum-rich areas appears. Detailed information gained by the physician and careful clinical examination allow the medical doctor to differentiate between these two diseases. In acanthosis nigricans, the lesions are dark-coloured, hyperkeratotic, papillary eruptions which are located on the neck and in the flexural areas, most often in obese patients with carbohydrate disorders and endocrinopathies. Grover disease usually affects older white men. The exacerbations occur mainly in the winter as it is assumed in connection with the intensified xerosis of the skin during this period of time. The clinical picture shows small papulovesicular eruptions, usually on the skin of the trunk, rarely on the proximal parts of the limbs, causing severe itching of the skin. Within papules, as in dyskeratosis follicularis, keratosis is often observed. The microscopic image is also similar to that of Darier

Table 1. Differential diagnosis of Darier disease: a summary box

Disease	Main clinical symptoms	Diagnostic tests
Darier disease	Skin: small and strongly corneous red-brown papules mainly in the seborrheic areas Nails: red and white longitudinal bands, subungual hyperkeratosis and V-shaped defects in the free margin of the nail Mucosal manifestation: whitish, clustered papules with central depression Secondary superinfections and malodour Itching +/-	Biopsy and histopathological examination (dyskeratosis, acantholysis)
Seborrheic dermatitis	Erythema covered with a white to yellowish oily scales in the sebum-rich areas Very common: 1–5% of the general population	Diagnosis based on clinical picture and examination
Acanthosis nigricans	Lesions are dark-coloured, hyperkeratotic, papillary eruptions which are located on the neck and in the flexural areas Often associated with diabetes mellitus, malignancy or PCOS	Laboratory tests (elevated glucose, cholesterol levels, triglycerides)
Transient acantholytic dermatosis (Grover disease)	Winter-associated exacerbations Small papulovesicular eruptions, usually on the skin of the trunk Severe itching of the skin Mainly seen in males over the age of forty	Diagnosis based on anamnesis, clinical and histopathological examination
Familial benign pemphigus (Hailey-Hailey disease)	Skin lesions of thin-walled flaccid, inflammatory plaques covered with erosions, scabs and papillary lesions Located primarily in the armpits, groins or anus Has to be differentiated with vesiculobullous type of Darier disease	Family history Clinical picture Histopathology examination
Pemphigus vegetans	Soft blisters and erosions being difficult to heal	DIF biopsy (direct immunofluorescence) Histopathology examination Pemphigus/pemphigoid antibodies

disease – with different degrees of dyskeratosis and acantholysis depending on the histological subtype of the disease. In Hailey-Hailey disease, the skin lesions of thin-walled flaccid, inflammatory plaques covered with erosions, scabs and papillary lesions are located primarily in the armpits, groins or anus. The essence of the disorder, as in Darier disease, is a genetically determined defect of the calcium ion transporting enzyme (ATP2C1), therefore family history is extremely important for diagnosis. Pemphigus vegetans is an autoimmune disease in which antibodies are directed against desmogleins responsible for cell connections within the epidermis. This results in the formation of soft blisters and erosions that are difficult to heal. In doubtful cases, immunofluorescence testing is required.

The linear variant of Darier disease requires differentiation from the linear verrucous epidermal nevus (ILVEN) and herpes zoster.

Treatment of Darier disease is symptomatic. Treatment possibilities can be divided into topical, oral and surgical and laser procedures. In a mild form of the disease with a small number of skin lesions and severe inflammation, low- and mid-potency topical steroids or topical preparations containing vitamin D are recommended. Good therapeutic effects were also observed after the use of 3% diclofenac in the form of a gel [4]. Topical retinoids (tretinoin, tazarotene and adapalene) are used to regulate hyperkeratosis. However, irritation of skin may occur. A great balance between exfoliation and moisturizers/emollient therapy should be maintained. Good therapeutic effects were also observed after topical application of 5% fluorouracil once a day [5]. Complete remission was observed after 3 weeks of treatment and lasted for 2–6 months.

Oral treatment is essential in some cases. Oral retinoids: acitretin, isotretinoin, alitretinoin are of the greatest importance. They are effective in nearly 90% of patients who experience worsening of the disease. They reduce hyperkeratosis and odour. However, a relapse after therapy withdrawal may occur. The most common adverse effects include mucosal dryness, epistaxis, hypersensitivity to sunlight, disturbances in kidney, liver and lipid profile. Therefore, the lipid profile and liver enzymes should be monitored during treatment. In addition, special care should be taken in women of reproductive age and in patients with comorbid psychiatric disorders. The recommended doses of acitretin are usually 10–25 mg/day, isotretinoin 0.5–1 mg/kg/day. Oral retinoids are not recommended in the intertriginous and vesiculobullous forms.

A beneficial therapeutic option in patients with contraindications to oral retinoid therapy may be the use of doxycycline. Sfecci *et al.* described the beneficial effect of using doxycycline at a dose of 100 mg/day for 4 weeks [6]. The anti-inflammatory effect of the antibiotic is mediated by the inhibition of metalloproteinase 9, which probably also plays a role in the pathogenesis of Darier disease [7]. Moreover, doxycycline may act in chelating calcium ions and facilitating their transport across cell membranes, thereby normalizing calcium stores and restoring proper connections in epidermal cells. Some reports confirm the effectiveness of oral prednisolone or cetirizine in the vesiculobullous form of disease [8].

In women experiencing exacerbations of the disease in the perimenstrual period, the use of oral contraceptives may be helpful.

Boehmer *et al*., based on a favourable response to low-dose naltrexone (LDN) in alleviating the symptoms of Hailey-Hailey disease, treated 6 patients with Darier disease. After 12 weeks of observation, two patients with mild to moderate disease had a clear clinical improvement. However, LDN was not effective in the group of 4 patients with the severe form of the disease [9].

In limited and hypertrophic forms of Darier disease, surgical methods, dermabrasion and laser therapy may be used.

Surgical treatment should be considered especially in patients unresponsive to conventional therapies. Ahcan et al. described a good therapeutic effect after surgical excision of the lesions in the buttock area in a 25-year-old patient not responding to oral retinoids [10]. Surgical methods, however, can provoke focal scarring and, if performed superficially, recurrence of the disease.

Raszewska-Famielec *et al.* [11] and Benmously *et al.* [12] described a favourable response to treatment with a fractional carbon dioxide (CO_2) laser performed on skin lesions in Darier disease patients. The mechanism of laser effectiveness in this condition remains unclear. It is possible that skin remodelling promotes the differentiation of keratinocytes and thus increases their adhesion. Other hypotheses assume the destruction of eccrine glands and thus the reduction of sweat exacerbating lesions [13]. Side effects include skin irritation a few days after the procedure.

Based on our experience, the outcomes of fractional CO_2 laser show significant improvement or complete remission. We observed that oral isotretinoin at a dose of 20–30 mg/day for 3–6 months before assuming the laser procedure gave better results in comparison to monotherapy by fractional CO_2 laser [14].

Other lasers, such as Er:YAG laser, pulse dye laser (PDL), diode laser, erbium-doped fibre laser (Er:YAG) were also suggested with different effects [15].

A few cases of patients treated with a photodynamic therapy (PDT) have been described [15]. The mechanism of action of photodynamic therapy in Darier disease is not fully understood. It is assumed that due to acantholysis occurring in the epidermis, the permeability of the photosensitizing agent is increased, which allows selective destruction of abnormal keratinocytes. In the case described by Avery *et al*., a significant improvement was achieved after two cycles of PDT. The improvement was

observed 27 months after treatment [15]. Exadaktylou *et al*. reported the use of PDT in a group of six patients with Darier disease [16]. Four of them, after the initial post-treatment irritation lasting 2–3 weeks, reported a permanent relief of symptoms or improvement, only one patient experienced a partial improvement, and one patient was unable to continue the therapy due to significant irritation. In the study, remission lasted from 3 months to 3 years [16].

Mucosal lesions in the course of Darier disease do not show a tendency to malignant transformation, thus their therapy is not required.

Currently no targeted therapies are available for patients with Darier disease. Therefore, the main goals for treatment are morbidity reduction and prevention of complications.

Among all advanced treatment possibilities, basic routine for such patients should include: infection treatment, moisturizing therapy, avoiding sunburn, high temperatures and mechanical injuries. In addition, topical and/or oral treatment may be sufficient. In many cases laser treatment can be the best option to obtain visible and quick reduction of lesions, which is the most important for patients suffering from Darier disease.

Conflict of interest

The authors declare no conflict of interest.

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