DARIER'S DISEASE - A PERSISTENT GENODERMATOSIS WITH A MAJOR PSIHOSOCIAL IMPACT

MARIA MOGA*,**, IULIA LEULESCU**, IRINA POPESCU**, CLAUDIA-IOANA DOGARU**, EMIL CĂTĂLIN POPA**, GRIGORE BĂLAN**, MIRCEA TAMPA*,**, SIMONA ROXANA GEORGESCU*,**

Summary

Darier disease is a rare autosomal dominant genodermatosis with onset in the first two decades of life. The classical form of Darier's disease is described in the literature as a persistent eruption of keratotic, hyperpigmented or red-brown papules with distribution in seborrheic and intertriginous areas. Although the severity of the pathology is variable, it usually has a chronic course with frequent exacerbations. We report on the case of a 41-year-old patient with Darier's disease with a typical pattern, moderate involvement and with a family medical history of Darier disease in a first-degree relative. Although clinically, the differential diagnosis can pose some problems, requiring the exclusion of other pathologies with a similar distribution, such as Hailey-Hailey disease or Grover's disease, the morphopathological diagnosis is the one of certainty in this situation. We emphasize the therapeutic challenges, since Darier's disease does not have a curative treatment, and remissions are frequent. The emphasis in this presentation is on the favorable therapeutic response, despite the low compliance, the anxious character and the psychosocial deterioration that impacted the patient's life along with the evolution of the disease.

Key words: *genodermatosis, persistent rash, chronic course, frequent exacerbations, therapeutic challenges, psychosocial deterioration, low compliance, anxious character.*

Received: 19.08.2024 *Accepted: 20.09.2024*

Introduction

Darier disease, known by many other names (Darier-White disease, follicular keratosis, follicular dyskeratosis), is a rare autosomal dominant genodermatosis whose onset is usually achieved during puberty [1][2]. It has a chronic and persistent course with exacerbations induced by exposure to the sun, heat, friction or infections [1]. With a prevalence of 1-4 per 100,000 people, the pathology has no ethnic predisposition, being able to affect all races and both sexes equally [1].

Etiopathogenically, Darier disease is characterized by mutations in the ATP2A2 gene resulting in dysfunction of the intracellular calcium ATPase SERCA2 with electrolyte accumulation in the cytosol [2][3]. Excessive intracellular calcium will cause acantholysis and apoptosis [2]. The classical form of Darier's disease is described in the literature as a persistent eruption of keratotic, hyperpigmented or red-brown papules with a tendency to confluence, with a predominant distribution in seborrheic and intertriginous areas [4]. Other manifestations can be repre-

* „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
** Dermato-venerology Department, Clinical Hospital for Infectious and Tropical Diseases „Dr.Victor Babeș" Bucharest, Romania.

sented by nail abnormalities, pitting of the palms and soles, and changes in the mucous membranes [1][4]. Since, like most genodermatoses, it is a disease with a major psychosocial impact affecting numerous organs and organ systems, often presenting exacerbations without periods of spontaneous remission, we chose to describe the following clinical case [2].

Case report

We report on a 41-year-old female patient, smoker, from an urban environment, known to have Darier disease and with family history of Darier disease in a first-degree relative (her father), who presented to the dermatology department of the Victor Babeș hospital for a exacerbation episode started about 3 weeks ago. The patient was diagnosed with Darier's disease in 2009 in our clinic, following the histopathological examination. Microscopic diagnosis was based on the finding of focal suprabasal acantholysis and dyskeratosis with the characteristic presence of eosinophilic "corps ronds"(round bodies) in the malpighian layer and "grains" (oval cells with collapsed keratin and parakeratotic nuclear debris) in the stratum corneum of the epidermis. Following topical and systemic corticosteroid treatment, skin lesions improved. In 2019, the patient returns to our clinic for an acute flare aggravated by the summer season, moment when it is decided to initiate the treatment with isotretinoin at a dose of 120 mg daily. In 2020, due to the marked xerosis that the patient complains about and the increase of transaminases twice above the normal value, it is decided to decrease the dose of isotretinoin to 80 mg daily, a dose that is also difficult to tolerate for our patient, but which shows a significant improvement of the appearance of skin lesions. Currently, the patient presents to our department with an eruption of red-brownish papules, covered with scales or crusts, with a tendency to confluence, disseminated at the level of the upper trunk, inframammary, retroauricular and frontal (Fig. 1, 2, 3). The papules are itchy, slightly painful and have an unpleasant odor. Also, nail changes are observed in the fingers of both hands such as longitudinal erythronychia, onychodystrophy, subungual hyperkeratosis and distal split nails in the shape of the letter "V" (Fig. 4). The patient states the aggravation of the pathology after the summer vacation where she was exposed to the sun for a long time without using a sun protection factor cream. She is hospitalized for treatment and specialized care. Following the blood tests, liver enzymes and serum lipids are within normal limits, for which it is decided to resume the systemic therapy with retinoids in a dose of 80 mg daily.

Discussions

Darier disease is a rare skin condition without curative treatment, the disorder being treated symptomatically [4]. The disease was originally described by the Englishman Prince Marrow in 1886, to be presented independently for the first time by Darier and White [5]. White was the first to recognize the genetic nature of keratosis follicularis, observing the condition in a mother and her daughter [2][5].

Darier disease is linked to the mutation in the ATP2A2 gene that encodes type 2 ATPase (SERCA2) of the endo/sarcoplasmic reticulum [6]. Malfunction of this gene causes aberrant epidermal keratinization and abnormal cell adhesion with desmosome clevage [2][6].

Since Darier's disease is characterized by hyperkeratotic papules in seborrheic regions, the disease can be easily misdiagnosed, leading to a delay in the correct treatment [6]. The differential diagnosis must consider other severe seborrheic dermatitis, Hailey-Hailey disease and Grover's disease, which often present lesions with a similar distribution [1]. However, Darier's disease is distinguished by the clinical involvement of the acral regions, nails and oral mucosa [1]. Family history can also be helpful, although due to its variable expression, a third of affected patients do not have relatives with this condition or they have a manifestation that went unnoticed [2][4]. Skin biopsy is necessary to confirm the diagnosis [1].

Follicular dyskeratosis can occur in two forms, which differ in their genotype and clinical picture [6]. Type I (segmental, linear) presents the lesions unilaterally, along the Blaschko's lines, while in the secon type (diffuse) the lesions are

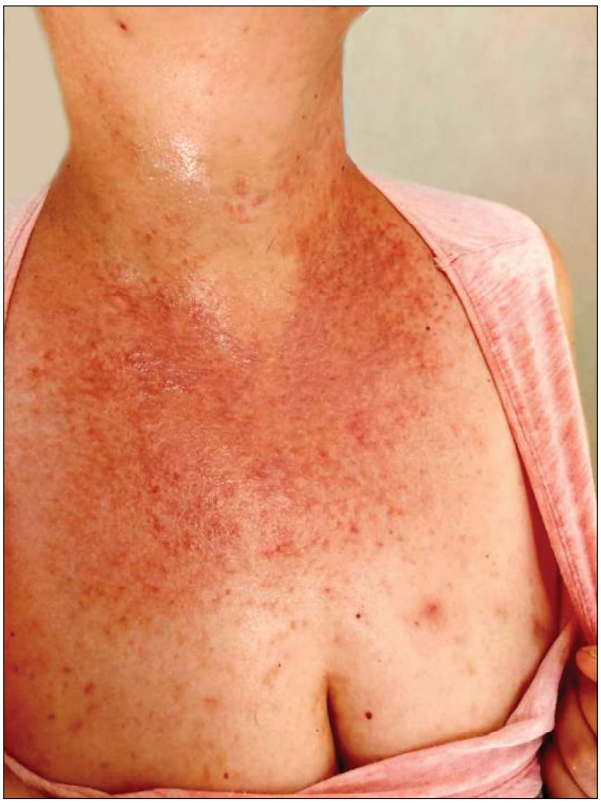

Figure 1 - Multiple red-brownish papules with a tendency to confluence, on an erythematous background, at the level of the upper trunk.

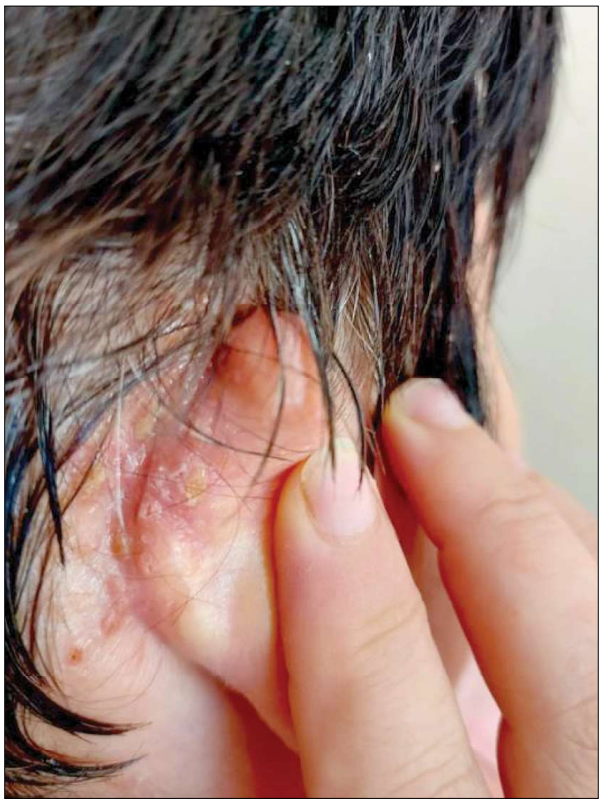

Figure 2 - Keratotic papules covered with scales and crusts on an erythematous background, located behind the year.

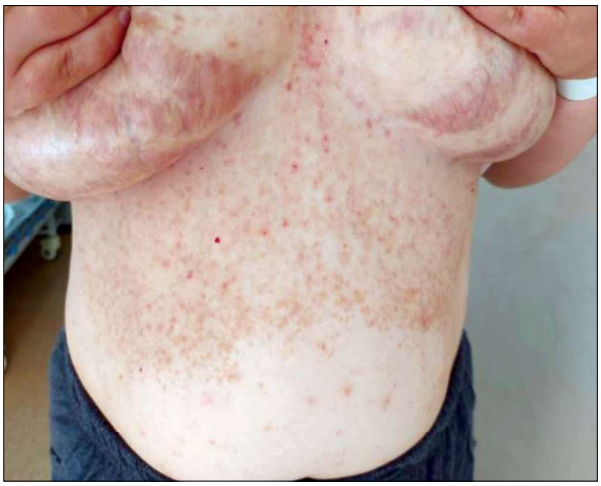

Figure 3 - Lesions with hyperpigmented maculopapular appearance, arranged inter- and inframammary.

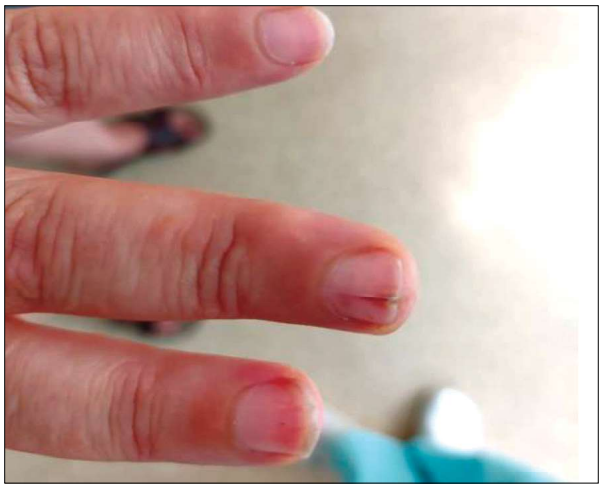

Figure 4 - Longitudinal erythronychia, distal V- shaped cleft of the third finger.

diffuse and bilateral, accounting for more than 90% of patients with this condition [6].

Although the severity of this pathology is variable, it usually has a chronic course with frequent exacerbations [1]. There is currently no treatment proven to be curative for Darier's disease; most cases are treated symptomatically to improve itching and irritation [7]. Daily use of emollients, cotton dressings and avoidance of exposure to moist environments and ultraviolet rays are recommended as general measures for all patients [1][7]. So far, there is no consensus on the treatment of Darier's disease, therefore no guidelines have been drawn up, leaving therapy to the discretion of the clinician. Often this is done depending on the experience of the attending physician and the extent of the disease [7].

For patients with mild to moderate disease, avoidance of triggers and regular use of urea or lactic acid emollients can often be sufficient as they treat hyperkeratosis and desquamation [1][4]. In acute flares, mid- to high-potency topical corticosteroids (groups 2 to 4) applied once or twice daily are preferred over topical calcineurin inhibitors [1]. Often they can be combined with local antibiotics in case of bacterial superinfections (gentamicin, mupirocin, fusidic acid) [1]. Preparations containing vitamin D (tecalcitol), 5-fluorouracil or 3% diclofenac gel have shown favorable therapeutic effects in recent studies [7]. Topical retinoids (tretinoin, tazarotene, adapalene), although more effective than corticosteroids in mild to moderate disease, should be used with caution alongside emollients and medium-potency corticosteroids (group 4), due to the risk of irritation and burning sensation [2][7].

Oral treatment is essential in severe cases, with retinoids such as acitretin, isotretinoin and alitretinoin being of considerable importance [4]. A beneficial therapeutic option in patients with contraindications to oral retinoids may be doxycycline; Sfecci et al. described its anti-inflammatory effects by inhibiting metalloproteinase 9 (considered to play a role in the pathogenesis of the disease) and by chelating calcium ions, thus normalizing calcium stores inside keratinocytes [11].

New studies demonstrate the possibility of extending therapy to diverse pharmaceutical classes [2]. Thus, Boehmer et al. emphasizes the efficacy of low-dose naltrexone (5mg/day) in mild-moderate disease, administering the opioid antagonist to 6 patients, 2 with moderate and 4 with severe disease. After 12 weeks of observation, the anti-inflammatory effect of naltrexone led to clinical improvement in the two moderately affected patients but not in the severely affected ones. The explanation may lie in the inhibitory effect on macrophage toll-like receptors, which naltrexone exerts at low concentrations [12].

In patients with severe generalized Darier's disease which is unresponsive to retinoids, therapy with systemic immunomodulators may be helpful. In a small case series of 3 patients with Darier disease with proven enhancement of the IL17/23 axis in lesional skin, antibodies such as secukinumab (anti-IL17) or guselkumab (anti-IL 23) induced a marked reduction in inflammation and papule flattening . In a single case report, JAK inhibitors such as oral baricitinib at a dose of 4 mg daily or low-dose immunoglobulin G resulted in resolution of lesions and marked reduction in pruritus [1].

A new pharmaceutical, miglustat (a glucosylceramide-synthetase inhibitor) used usually in conditions such as Gaucher and Niemann-Pick disease, appears to have a promising future in the treatment of Darier's disease. Remarkably, this pharmaceutical chaperone appears to restore mature intercellular junctions (adherens junctions and desmosomes) at the level of keratinocytes, thus enhancing intercellular connections within the epidermis and restoring the skin barrier [13].

In selected cases, physical therapies such as dermabrasion, (electro)surgical excision, CO2/erbium/pulsed dye laser ablation, photodynamic therapy or radiation therapy are methods of choice [7]. Injection of botulinum toxin type A once every 6 months into the intertriginous areas is also used successfully, helping to reduce symptoms of discomfort [5][7].

A 2021 study by the Indian Journal of Dermatology, Venereology and Leprology conducted a literature review of articles describing various treatments for Darier's disease. It was

performed using PubMed and included a total of 68 articles: 3 prospective studies, 44 case reports/ case series and 21 letters/correspondence/ clinical images that described topical, oral or physical treatments. The conclusion of this study was that retinoids and fluorouracil were the most effective topical therapies, while oral retinoids proved successful in generalized disease. Last but not least, for localized and resistant lesions, physical therapies such as laser ablation, dermabrasion or surgical excision have been the first-line therapy [7].

Although Darier's disease is a pathology with predominantly cutaneous manifestations, we consider it essential to recognize among dermatologists the neurocognitive and neuropsychiatric symptoms that often accompany the clinical picture [8][9]. As the ATP2A2 gene is the one responsible for the pathogenesis of the disease and as it is highly expressed both in the skin and in the brain, its possible pleiotropic effects could be explained by the common ectodermal origin of these tissues and by the involvement of intracellular calcium signaling in neuronal excitability, neurotransmission and synaptic plasticity [8]. Thus, neurological conditions such as epilepsy, mental retardation or learning disabilities have been described in association with Darier's disease [4][8]. Psychiatric manifestations are more common and involve the occurrence of depression (most commonly observed), anxiety and bipolar syndrome [8]. A Swedish population-based study conducted in 2015 assessed the occurrence of psychiatric syndromes among individuals with Darier compared to unaffected individuals in the general population. It concluded that individuals with Darier have a 4.3 times higher risk of developing bipolar disorder and a 2.3 times higher risk of developing schizophrenia compared to the unaffected general population. The risk of depression was not quantified in the study, but it is expected to substantially exceed the values of other psychiatric disorders [10].

Refferal to genetic services may be an appropriate approach, especially for the patients who want to conceive, as the risk of haveing a child also affected is 1 in 2 (50 %) [1].

Conclusions

Although it is a pathology with predominantly cutaneous manifestations, Darier's disease must be seen as a condition with multi-organ involvement, and the neuropsychiatric symptoms that are often associated must be considered and integrated in the clinical context. Superinfections with bacterial, fungal or viral species that cause an unpleasant odor can be another considerable source of distress. Anxiety and depression with consequent decrease in treatment compliance can ultimately represent major obstacles. Patients with Darier disease have a normal life expectancy, although their quality of life can be significantly affected, and the psychosocial impact of the pathology can lead to social isolation over time.

Bibliography

1. Chyl-Surdacka K, Borzęcki A, Latifa J, TurskaKozłowska M, Majchrzycka M. Keratosis follicularis (Darier disease) - clinical characteristics and treatment – a review and update. *Postepy Dermatol Alergol.* 2023;40(3):337-340
2. Haber, R. N., & Dib, N. G. (2021). Management of Darier disease: A review of the literature and update. In *Indian Journal of Dermatology, Venereology and Leprology* (Vol. 87, Issue 1). https://doi.org/10.25259/IJDVL_963_19
3. Li Pomi, F., Motolese, A., Bertino, L., Macca, L., Arminio, N. C., Cardia, R., Vaccaro, M., & Borgia, F. (2021). Beyond the skin involvement in Darier disease: A complicated neuropsychiatric phenotype. *Clinical Case Reports,* 9(6). https://doi.org/10.1002/ccr3.4263
4. Curman, P., Bern, J., Sand, L., Cederlöf, M., Bachar-Wikström, E., & Wikström, J. D. (2021). Patients with darier disease exhibit cognitive impairment while patients with hailey-hailey disease do not: An experimental, matched case-control study. *Acta Dermato-Venereologica,* 101(6). https://doi.org/10.2340/00015555-3818
5. Cederlöf, M., Bergen, S. E., Långström, N., Larsson, H., Boman, M., Craddock, N., Östberg, P., Lundström, S., Sjölander, A., Nordlind, K., Landén, M., & Lichtenstein, P. (2015). The association between Darier disease, bipolar disorder, and schizophrenia revisited: A population-based family study. *Bipolar Disorders,* 17(3). https://doi.org/10.1111/bdi.12257
6. Sfecci A, Orion C, Darrieux L, et al.. Extensive Darier disease successfully treated with doxycycline monotherapy. *Case Rep Dermatol* 2015; 7: 311-5.

7. Boehmer D, Eyerich K, Darsow U, et al.. Variable response to low-dose naltrexone in patients with Darier disease: a case series. *J Eur Acad Dermatol Venereol* 2019; 33: 950-3.
8. Savignac M, Simon M, Edir A, Guibbal L, Hovnanian A. SERCA2 dysfunction in Darier disease causes endoplasmic reticulum stress and impaired cell-to-cell adhesion strength: rescue by Miglustat. *J Invest Dermatol.* 2014 Jul;134(7):1961-1970.

Conflict of interest
NONE DECLARED

Correspondance address: Mircea Tampa
„Carol Davila" University of Medicine and Pharmacy Bucharest, Romania
Dermato-venerology Department, Clinical Hospital for Infectious and Tropical Diseases „Dr. Victor Babeş"
Bucharest, Romania
e-mail: mircea.tampa@umfcd.ro