Bulletin of the *Transilvania* University of Braşov.
Series VI: Medical Sciences • Vol. 11 (60) No. 1 - 2018

DARIER'S DISEASE IN TWINS - CASE REPORT AND REVIEW OF THE LITERATURE

L.G. FEKETE[1] M. IRIMIE[2*] A. GALL[1] L. FEKETE[1]

Abstract: *Darier's disease is a rare genomic autosomal dominant disease characterized by keratinization disorders with primary localization in the hair follicle. The causative gene is located at chromosome 12, region 12q23-24.1. and encodes the SERCA2-ATP-ase enzyme that has a role in calcium homeostasis, subsequently causing keratinization disorders. We present the clinical case of two 42-year-old twin women with typical lesions of the disease. The histological and genetic examination of one of the patient has confirmed the clinical diagnosis of Darier's disease. The prevalence of the disease has been estimated at about 1:55.000, no concrete data with regards to the occurrence rate of it amongst twins being published. We have found four clinical cases in which the disease occurred amongst twins, the key feature of the presented cases being the rare occurrence of Darier's disease.*

Key words: *Darier's disease, keratosis follicularis, genodermatoses.*

1. Introduction

Darier's disease is a rare genomic autosomal dominant disease characterized by keratinization disorders with primary localization in the hair follicle. Partly described by Lutz in 1860 as hypertrophic acne sebaceous and by Lebert in 1864 under the name of sebaceous ichthyosis, the affection is personalized by Darier in 1889 under the name of vegetative follicular psorospermosis, describing its clinical picture and histological aspect. Simultaneously, White, in 1889, using the term follicular ichthyosis, presents the same clinical description. White suspects the genetic substrate of the disease describing a familiar aggregation of it [17]. The causative gene is located at chromosome 12, region 12q23-24.1. and encodes the SERCA2-ATP-ase enzyme that has a role in calcium homeostasis resulting in impairment of intracellular transport of

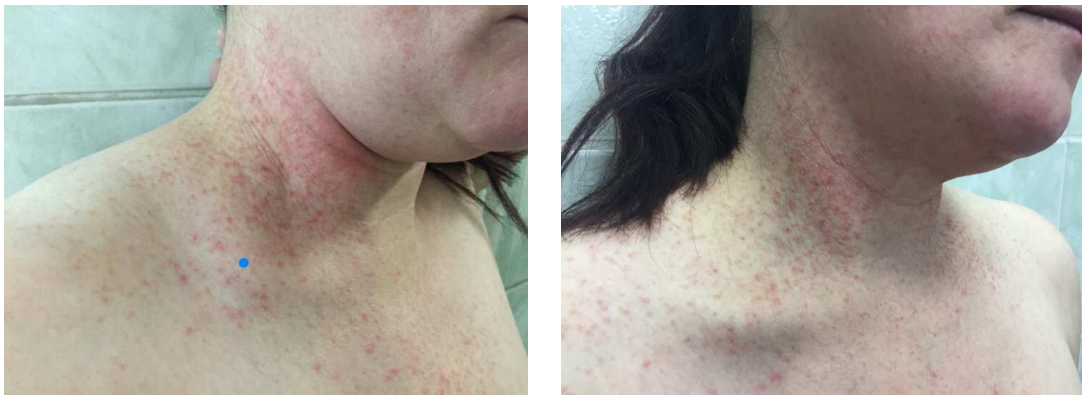
1 [1]University of Medicine and Pahrmacy, Tîrgu Mureș, România
[2]Transilvania University of Brașov, Faculty of Medicine, România
*Corresponding author: Marius Irimie. E-mail: <marius_irimie2002@yahoo.com>

calcium and of the calcium-signaling pathway, subsequently causing keratinization disorders [2], [11], [19]. Mutations in the ATP2A2 gene are the cause of the disease with a penetrance estimated at over 95%, although gene expressivity is variable [8], [9], [18]. Most of the reported cases are familiar. Sporadic cases have been reported in literature, one study group pointing out the lack of a positive family history in 47% of patients [3]. Only a few cases of Darier's disease were described in twins.

2. Clinical cases

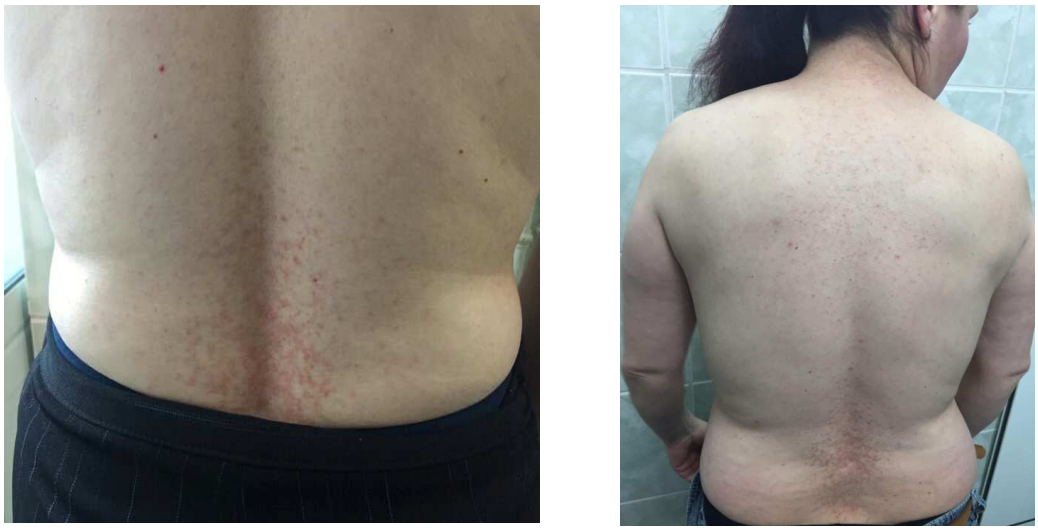
We present two 42-year-old twin women with slightly protruding keratotic papules, some of which confluent in yellowish-brown, pruritic plaques, localized in the lumbosacral, laterocervical, sternal and axillary areas that worsen in heat, sweat and sunlight. These lesions have appeared progressively since the age of 20 at both patients. Patient no. 1 also presents nail changes manifested by white longitudinal striations, and keratoderma of the palms. Epilepsy, depressive states with multiple suicidal attempts and hypothyroidism were diagnosed in patient no. 1. Patient no. 2 exhibits no nail changes and presents obesity, depressive states and severe dislipidemia confirmed by the laboratory analyses (*Figures 1, 2 and 3*). From the familial history we have found that the patients' mother showed the same type of skin lesions developed at the same age, but a certainty diagnosis was never identified. The histological examination has confirmed the clinical diagnosis in both patients. Histopathological examination reveals: dyskeratosis with round body formation and eosinophil grains, suprabasal acantholysis with a suprabasal over-cleavage and gaps formation. Other changes were papillomatosis, acanthosis, and hyperkeratosis with a chronic inflammatory infiltrate in the dermis (*Figure 4*).

Genetic examination in patient no. 1 evidenced the mutation C560R, located in the ATP-binding domain, which decreases the protein expression of SERCA.



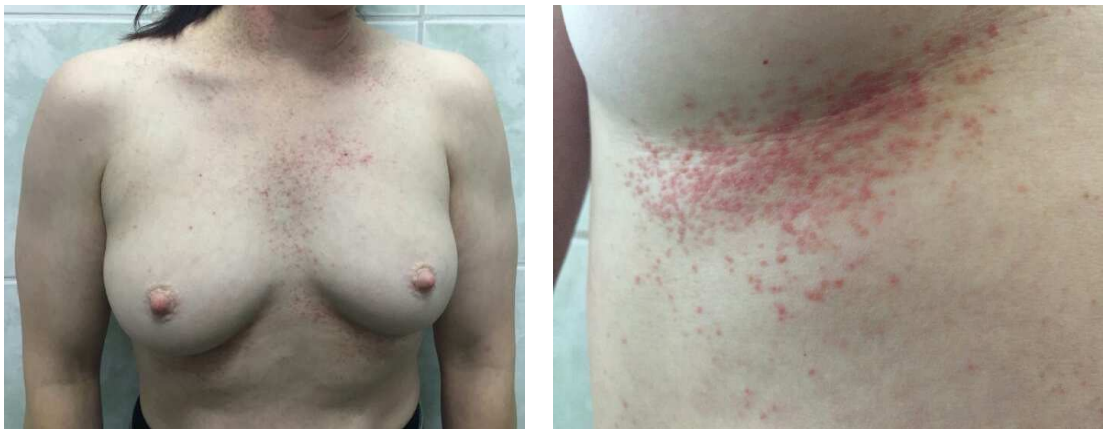
Patient no. 1 Patient no. 2

Fig. 1. Clinical aspect of laterocervical area



Patient no. 1 Patient no. 2

Fig. 2. Clinical aspect - lumbosacral area



Patient no. 1 Patient no. 2

Fig. 3. Clinical aspect of sternal and axillary areas

In future we would like to perform the genetic examination for patient no. 2, as well. The patients followed systemic treatment with isotretinoin initially at a dose of 0.5 mg/kg/day for four months, continuing with a maintenance dose of 0.3 mg/kg/day with favorable results in a few weeks. Since the detection of the disease the patients suffered two recurrences, approximately in the same time, favorably treated with systemic retinoid and local exfoliating and moisturizing creams.

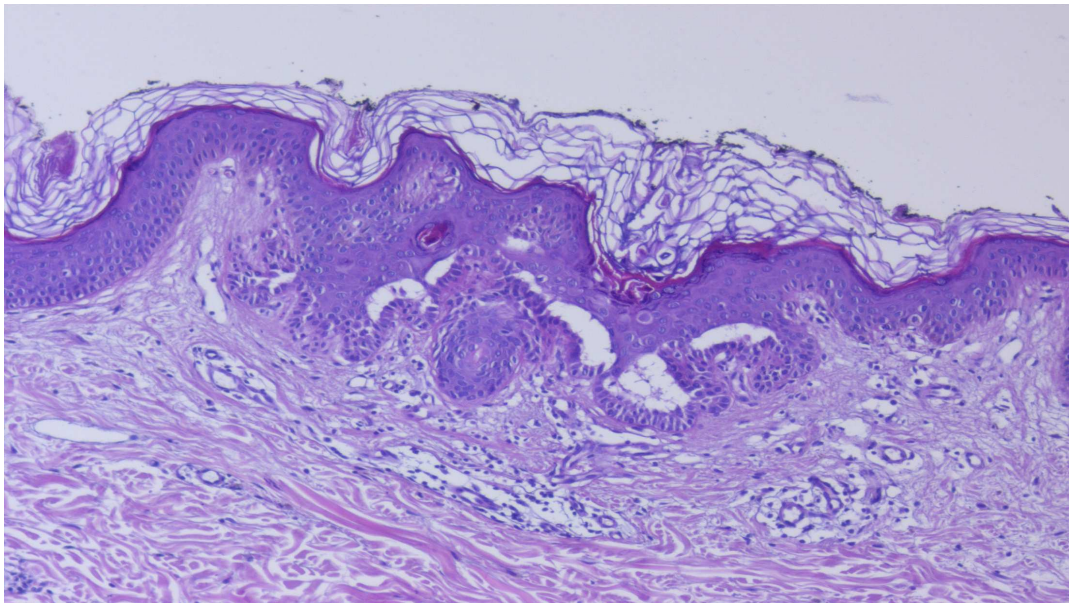


Fig. 4 Patient no. 1 - Histopathological aspect. H&E stain 10x

3. Discussion

Worldwide, the prevalence of the disease has been estimated at about 1:55,000, ranging 1 case at 26,300 inhabitants in Slovenia and 1 case at 30-35,000 inhabitants in Northern England and Scotland [4]. Concerning the incidence of the disease in twins no data is published. A thorough review of the literature was performed using international database search. We have found four clinical cases in which the disease occurred amongst twins [5], [6], [14], [16]. The disease appears in childhood or most frequently in adolescence, around the age of 20 years, like in our presented case. Although both gender are affected, the disease was mostly predominant among males. In 47% of the cases, no positive history of the disease was found, these being considered as a sporadic mutation. In the presented case, the patients' mother showed the same type of skin lesions developed at the same age, without a specific diagnosis of Darier's disease. We consider a family aggregation of the disease in our case. The evolution of Darier's disease is chronic. In one third of the cases the illness improves progressively, and in another third it gets worse with the age. The disease presents improvements and exacerbations for longer or shorter periods of time, being influenced by various external factors such as: sun, ultraviolet, trauma, sweating [4], [7]. Differential diagnosis is done with: acrokeratosis veruciformis Hopf, Hailey-Hailey disease, perforating dermatosis, Grover disease, seborrheic dermatitis, acanthosis nigricans, pemphigus vegetans, eczema, psoriasis, etc [10]. Complications may occur such as bacterial superinfections, viral, especially herpetic and fungal infections. Darier's disease can be associated with a series of comorbidities of a neuropsychiatric nature like learning disorders, mental retardation, bipolar disorder, schizophrenia, epilepsy and various other

abnormalities like diabetes, metabolic disturbances, bone cysts, etc. like those presented in our case [15], [20]. The treatment has a palliative character, including preventive methods (photoprotection, emollients, local anti-inflammatory and antiseptic agents), topical and systemic medical therapy (retinoids, corticosteroids, 5-fluorouracil), as well as multiple surgical alternatives (dermabrasion, electrotherapy, laser treatment, photodynamic therapy, surgical excision) [1], [12], [13].

4. Conclusion

Darier's disease is a rare genomic autosomal dominant disease characterized by keratinization disorders with primary localization in the hair follicle which is caused by mutations in the ATP2A2 gene that encodes the Sarco/Endoplasmic Reticulum Ca2+-ATPase type 2 isoform (SERCA2), resulting in impairment of intracellular transport of calcium and of the calcium-signaling pathway. The disorder is frequently associated with neuropsychiatric, endocrinological and metabolic conditions, and knowing the importance of the neuronal calcium-signaling pathway it has drawn the attention to the relationship between cutaneous diseases and these disorders – namely the possibility that they represent an expression of the same genetic anomalies, an idea that should be explored in future. The specificity of the presented cases is the rare occurrence of Darier's disease at twins.

References

1. Ayres, S., Jr. *Darier's disease responds to the synergism of vitamins A and E*. In: Int J Dermatol. 1985, Vol. 24(1), p. 65-67.
2. Bashir, R.., Munro, C.S., Mason, S., et al.: *Localisation of a gene for Darier's disease*. In: Hum. Molec. Genet., 1993, Vol. 2, p. 1937–1939.
3. Beck, A.L., Finocchio, A.F., White, J.P.: *Darier's disease: a kindred with a large number of cases*. In: Brit. J. Derm., 1977, Vol. 97, p. 335–339.
4. Burge, S.M., Wilkinson, J.D.: *Darier-White disease: a review of the clinical features in 163 patients.* In: J Am. Acad. Derm. 1992, Vol. 27, p. 40–50.
5. Cernohorsky, J.: *Follicular keratosis in twins.* In: Cesk Dermatol. 1961, Vol. 36, p. 86-90.
6. Fortier, P., Delestre, I., Eon, F., et al.: *Recurrent viral superinfection in Darier's disease in twin sisters*. In: Ann Dermatol Venereol. 1979, Vol. 106(11), p. 919-921.
7. Godic, A.: *Darier's disease. A review of pathophysiological mechanism.* In: Acta Dermatoren., 2003; Vol. 12, p. 119-123.
8. Yoneda, K., Demitsu, T., Kubota, Y.: *Novel ATP2A2 mutation in a patient with Darier's disease*. In: J Dermatol 2014, Vol. 41, p. 349-350.
9. Green, E.K., Gordon-Smith, K., Burge, S.M., et al.: *Novel ATP2A2 mutations in a large sample of individuals with Darier disease*. In: J Dermatol 2013; Vol. 40, p. 259-266.
10. Hulatt, L., Burge, S..: *Darier's disease: hopes and challenges*. In: J R Soc Med. 2003, Vol. 96, p. 439-441.
11. Kaibuchi-Noda, K., Sugiura, K., Takeichi, T., et al.: *Darier's Disease: A novel ATP2A2 missense mutation at one of the calcium-binding residues*.

In: Acta Derm Venereol., 2015, Vol. 95, p. 362-363.
12. Krakowski, A.C., Nguyen, T.A., Eichenfield, L.F.: *Treatment of Segmental Keratosis Follicularis (Darier Disease) Using Ablative Fractional Laser Resurfacing*. In: Dermatol. Surg. 2015, Vol. 41(4), p. 516-518.
13. Mohamed, K.N.: *Darier's disease: response to combination of vitamins A and E.* In: Singapore Med J., 1987, Vol. 28(1), p. 80-82.
14. Mohd, K.N.: *Darier's disease in twins*. In: Int J Dermatol., 1984, Vol. 23(5), p. 339-340.
15. Nakamura, T., Kazuno, A., Nakajima, K., et al.: *Loss of function mutations in ATP2A2 and psychoses: A case report and literature survey*. In: Psychiatry Clin Neurosci., 2016, Vol. 70, p. 342-350.
16. Nishioka, M., Bundo, M., Ueda, J., et al.: *Identification of somatic mutations in monozygotic twins discordant for psychiatric disorders*. In: NPJ Schizophr. 2018, No.13; Vol. 4(1), p. 7-9.
17. Rook's Textbook of Dermatology, 8th ed. Disorders of Keratinization. *Darier's Disease and Related Disorders. Darier's disease.* In: Wiley-Blackwell Publishing, Oxford 2010; Vol. I (19), p. 81-86.
18. Sakuntabhai, A., Burge, S., Monk, S., et al.: *Spectrum of novel ATP2A2 mutations in patients with Darier`s disease*. In: Human Molecular Genetics, 1999, Vol. 8, p. 1611-1619.
19. Sakuntabhai, A., Ruiz-Perez, V., Carter, S., et al.: *Mutations in ATP2A2, encoding a Ca2+ pump, cause Darier disease*. In: Nat Genet. 1999, No. 21, p. 271-277.
20. Takeichi, T., Sugiura, K., Nakamura, Y., et al.: *Darier's disease complicated by Schizophrenia caused by a novel ATP2A2 mutation*. In: Acta Derm Venereol. 2016, Vol. 96, p. 993-994.