DARIER-WHITE DISEASE: GENETIC DETERMINISM FOR VESICULOBULLOUS REACTIONS

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Abstract

Darier disease is an autosomal dominant disease, with severe simptoms and an early onset, during childhood, with a relatively rare incidence, of one reported case in 55 000 healthy individuals. The clinical aspect implies the presence of a symmetrical eritematous eruption, in the upper trunk, face and lateral cervical aspects, consisting in the presence of yellow brownish skin scales and keratotic papules. We present the case of a 12 years old boy diagnosed for the first time with Darier-White disease showing an eruption on the forehead, perioral and lateral cervical skin, with onset at 7 years old, remaining untreated since – while the mother and his step-brother, undiagnosed, suffered from the same condition with identical distribution. Histopathological examination reveals discohesive dyskeratocytes, the presence of corps ronds and suprabasal clefts. The inheritance pattern in our case suggests etiological ATP2A2 typical mutation involvement along with the action of stress cutaneous factors as ultraviolet B radiation.

Keywords: Darier Disease, forehead, inheritance pattern, mutation, skin

Introduction

Darier-White disease (DWD), also known as kertosis follicularis, is a rare and severe inheritable disease, with an autosomal dominant pattern, having an estimated prevalence of 1 in 55 000 normal individuals, accompanied by a considerable handicap. The disease was first reported independently by Darier and White in 1889, being the first to recognize the genetic nature of keratosis follicularis, also noticing that a mother and her daughter were both afflicted. Clinically, the disease is characterized by the existence of keratotic papules in seborrheic skin areas, located, especially, in trunk face and skin foldings. Furthermore, infections occur frequently in affected regions, thus, being considered a major discomfort for the patients. The disease typically presents with puberty onset, a chronic relapse, and exacerbations favored by UV irradiation, heat, friction and infections [1].

Materials and methods

A 12 years old boy presented to the dermatologist in our hospital with the presence of cohesive, keratotic papules on the forehead, having a brownish color, non-homogeneously spread involving the surrounding skin, condition that initially manifested at the age of 7 years old. The mother, aged 46 years old, stated that she also suffered from a similar condition, which she left untreated, started from the age of 10 years old following an apparent remissive pattern with the same distribution. The boy has a normal syster born, while his mother during her previous marriage gave birth to another male now aged 27 years old that is afflicted by the same condition. The latter has another stepsister (figure 1) from the mother's first husband that showed no signs of the disease.

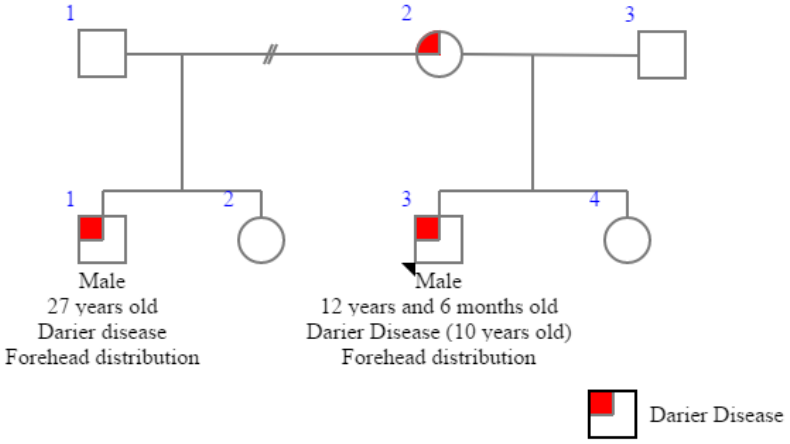

Figure 1. Pedigree chart for the presented case – with arrow, is the proband; 1-2 is the mothers first relationship, now divorced, while 2-3 depicts actual marriage.

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Results

At close inspection, on the forehead, bilateral cervical, around the mouth and nose skin, it was observable a rugged eruption with eritematous and papular appearance covered in yellowish to brown scales. In our case, a representative lesion was sampled, consisting in a cutaneous biopsy (0.4/0.4 cm) with emergent hair shafts and brownish areas (figure 2). The fragment was processed via automated standard haematoxylin and eosin stains, consisting in successive and progressive concentrated ethylic alcohol baths of 70%, 80%, 96%, 99% with isopropyl intermediaries. Following paraffin embedding and chemical processing, microtome histological sections with 2.5µm in thickness were made. The optical microscopic examination revealed an acantholytic, dyskeratotic epidermis, with basophilic discohesive dyskeratocytes, conspicuous nuclei and nucleolus, frequently surrounded by a perikarional halo. Suprabasal clefts filled by haematic infiltrates were visible (figure 3 and 4), a conspicuous lymphocytic inflammation with admixed neutrophils and oedema, probably, due to an over-added infectious process in the biopsy region of interest. The dermis revealed actinic elastosis, thus, proving the existence of repeated, prolonged, ultraviolet irradiation (figure 5).

Figure 2. Macroscopic appearance of cutaneous biopsy for the case in matter (0,4/0,4 cm, buffered formalin 0,4%).

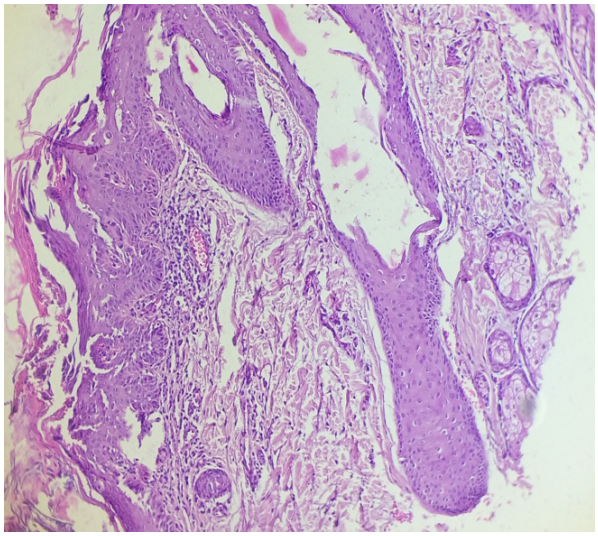

Figure 3. Blistering-like suprabasal clefts, acantholysis and frequent diskeratocytes are visible; brisk upper dermis inflammatory infiltrate (HE, 4x10).

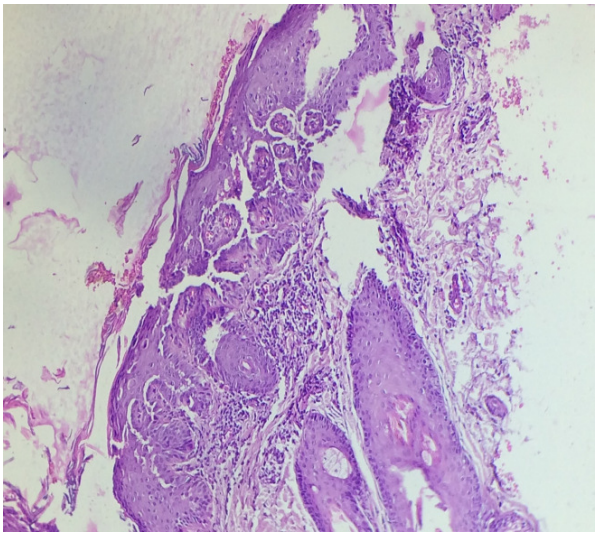

Figure 4. Suprabasal clefts in parakeratotic epidermis, disruption of rete ridges and pearl-like structures with frequent diskeratocytes - corps ronds - surrounded by inflammatory infiltrate (HE, 4x10).

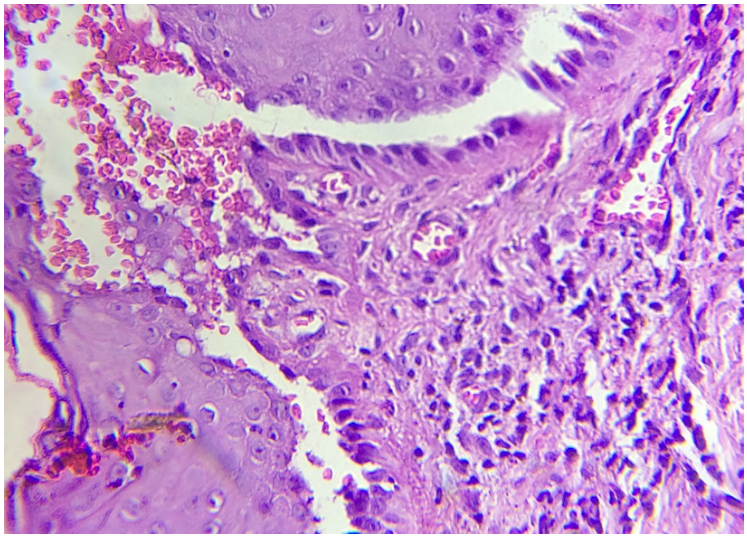

Figure 5. Structural details of corps ronds in the neighbouring of a suprabasal cleft: basophilic cytoplasm, discohesivness, nuclei with halo; notably lymphocytic inflammation with rare neutrophils – infection – hyperemia and oedema in upper dermis (HE, 40x10).

Discussion

The genetic inheritance of DWD is conditioned by a heterozygous mutation in the ATP2A2 gene, which encodes the sarcoplasmic reticulum Ca2+-ATPase-2 (SERCA2), located in the 12th chromosome, region 12q24.11, with an autosomal dominant pattern and high penetrance that exceeds 95%. Because the disease is causing mutations in ATP2A2 that afflicts functional domains of the gene, the mechanism of autosomal dominant transmission is believed to be haploinsufficiency, thus, one wild-type functioning isoform of ATP2A2 gene remaining insufficient to compensate DWD specific injuries. The expression of isoforms ATP2A2a and ATP2A2b, evidenced by hybridizing northern blots containing specific probes for 3' un-translated ends of both genes, have strong intensity signal in keratinocytes for a 4.5-kb length, but also in hearth and skeletal muscles [2]. More than 130 mutations were identified, including frameshift and in-frame deletions, insertions, splice-site mutations, and non-conservative missense in functional domains, thus, disclosing the role for SERCA2 in Ca2+ signaling pathways for cell-to-cell adhesion regulation and differentiation of the epidermis layers [3]. However, some cases present mutations located in exon 21 which is specific for SERCA2b resulting in a loss of expression sufficient enough to cause a DWD pathological phenotype. The fact that SERCA2b, encoded by ATP2A2b, cannot be compensated by SERCA2a expressions allows us to conclude that SERCA2b remains the main epidermal isoform [4]. As a result of the loss SERCA2 Ca2+ transport on Ca2+ homeostasis, DWD specific keratinocytes display lower endoplasmic reticulum (ER) Ca2+ concentrations [5]. Thus, compensatory mechanisms are activated consisting in the up-regulation of transient receptor potential canonical channel 1 (TRPC1) resulting in restricting apoptosis together with the up-regulation of ATP2C genes that encodes Ca2+/Mn2+-ATPase, a Ca2+ pump for the Golgi apparatus, that have similar effects of TRPC1 [6]. It seems that Ca2+ depletion of ER stores has the potential to impair post-translational modification in protein secretion triggering a ER stress response, easily augmented by external stressors like ultraviolet B irradiation, heat, infection and frictions. Meanwhile, inflammation and cytokines down-regulate ATP2A2 activity, therefore, DWD keratinocytes being unable to overcome the ER stress because of defective up-regulation of SERCA2 expressivity resulting in premature induced apoptosis. The cumulative and final result of these molecular impairments is the histological appearance of apoptotic keratinocytes observed in DWD, known also as "corps ronds" [7]. Nonetheless, impairment of SERCA2 pumps affects the molecular assembly of the desmosomes complex, the trafficking of desmoplakins, desmogleins and desmocollin represented by their significantly inhibition in DWD keratinocytes. The summative result of this inhibitions marks the microscopic acantolysis, suprabasal clefts, abnormal keratinization or dyskeratosis [4]. Pharmacologically, the α-glucosidase inhibitor miglustat restores mature adherens junctions and desmosomes in DWD keratinocytes, thus, increasing adhesion strength. It has been suggested that restoration of nonmutated proteins due to miglustat favorable response in DWD might imply a misfolding mechanism in the ER [8]. In order to have a competent diagnosis, the clinician should rely on the macroscopic appearance of DWD rely that consists in symmetrical distribution of red-brown keratotic papules, unilateral or localized, that turn almost verrucoid if sufficiently close together. On seborrheic areas and in flexures, greasy, malodorous papules and plaques may be also observed. Sometimes, oral mucosa may become involved in the lesions, while nails may show subungual

hyperkeratosis, fragility and splintering, with alternating white and red longitudinal bands. Microscopic examination on standard hematoxylin and eosin stains reveals acantholytic dyskeratosis, with proeminent irregular acanthosis and papillomatosis, suprabasal clefts and dyskeratotic, basophilic cells with large nuclei, sometimes with a perinuclear hallo. If present in the granular layer, these basophilic cells define the presence of corps ronds. During infections of interested areas a brisk upper dermis infiltrates of lymphocytes becomes visible with haemorrhage that my spill inside the suprabasal clefts. Differential diagnosis includes the variant Hailey-hailey disease, in which the full thickness of epidermis becomes subject to acantholysis with scant dyskeratocytes, and transient acantholytic dermatosis as well as all other blistering dermatoses, in which rete ridges are sometimes spared with predominant spongiosis [1].

Conclusions

As in many situations, DWD seems to be a clear example of a genetic determinant in pathologic cutaneous lesions. Mutations found in ATP2A2 isoforms, even in a heterozygous trait, seem to predict the appearance of DWD in future children. Early onset, high cutaneous sensitivity to external stress factors, and superimposed infections reveals DWD as a disease accompanied by a high distress for the young patients regarding self-esteem and cosmetic features. The fact that treatment is available, at least partially effective, for these patients is an important reason for further research in SARC2 and ATP2A2 genes relationship in tissue development and homeostasis.

Aknowledgements

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Conflict of interests

The author declares no conflict of interests.

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards depicted in the Helsinki Declaration, as revised in 2000, as well as the national law regarding medical publications and tissue manipulation.

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