IN-DEPTH REVIEW

Molecular Pathogenesis and Complications Associated with Keratosis Follicularis: A Clinical Review

Hira Ghani, BA[1], Stefani Cubelli, DO[2], Raphia K. Rahman, BA, MBS[3], Alexandra Chervonsky, BA, MA[1]

[1]New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY
[2]St. John's Episcopal Hospital, Far Rockaway, NY
[3]Rowan School of Osteopathic Medicine, Rowan, NJ

ABSTRACT

Keratosis follicularis or Darier's disease (DD) is a rare autosomal dominant disorder characterized by the appearance of multiple scaly papules affecting seborrheic areas. It is a multisystem disorder that occurs in the first or second decade of life, and extends beyond cutaneous involvement. It has been reported to be associated with various basal cell carcinoma (BCC) and other skin cancers, nail changes, ocular/mucosal manifestations and neuropsychiatric disorders. Additionally, individuals with DD have a greater risk of being diagnosed with Type 1 Diabetes Mellitus as well as disease-specific risk of heart failure. The goal of this review is to explore the molecular pathogenesis of keratosis follicularis, and to investigate the extent and severity of various complications associated with this condition. Furthermore, dermatologic practice recommendations will be reviewed for the management of DD.

INTRODUCTION

In 1889, Dr. James C. White, a professor of Dermatology at Harvard University published the first case report of a patient with Keratosis Follicularis, whose skin appeared to be occupied with a variety of lesions, some of which were the "size of a pinhead, smooth and firm", while others were slightly larger, but similar in appearance. The same year, independently from Dr. White in Paris, Dr. Darier published another case report of a patient with a similar presentation. Keratosis follicularis or Darier's disease (DD), a rare autosomal dominant disorder, is characterized clinically by the appearance of multiple, pruritic, discrete, scaly papules affecting seborrheic areas coupled with palmar pits, nail changes and mucosal involvement.[1]

These hyperkeratotic papules can be present on the middle of the chest, upper shoulders, neck and face.[2] The papules coalesce into plaques which can appear papillomatous and may become hypertrophic, malodorous, painful and prone to secondary infections.[2, 3] The disorder is a relatively common genodermatosis and affects approximately 1 in 36,000 individuals. It is characterized by late age of onset and typically presents in the first or second decade. Histologically, DD is characterized by the presence of dyskeratotic cells, also known as corps rounds, which are small round keratinocytes with basophilic nuclei, and acantholysis–loss of intercellular connection between keratinocytes.[3]

Topical tazarotene, topical isotretinoin, topical adapalene and oral retinoids have been reported to be effective for the treatment of mild-to-moderate keratosis

follicularis.[4-6] Surgical options for severe or refractory disease include dermabrasion, carbon dioxide laser, and Neodymium-doped Yttrium Aluminum Garnet (YAG) laser. [7] More recently, the role of naltrexone has also been explored in treating DD. While low-dose naltrexone has been quite successful in treating Hailey-Hailey disease, a genodermatosis similar to DD with a genetic mutation coding for a loss of function of a Ca^{2+} -ATPase pump (hSPCA1-pump), it has shown worsening of symptoms after initial treatment when used for severe DD.[8] However, low-dose naltrexone has been an effective and viable treatment option for the treatment of mild-to-moderate spectrum of DD.[8] Further, DD may be exacerbated by ultraviolet light exposure, particularly ultraviolet B, as well as by heat, humidity, and friction. Additionally, the use of topical sunscreens and ascorbic acid have been shown to be effective in the prevention of disease flares.[9]

DD has been reported in association with non-melanoma skin cancers (NMSC), including various basal cell carcinomas (BCC), as well as neuropsychiatric disorders such as Bipolar disorder.[10, 11] Moreover, rare cases involving nail changes and ocular manifestations have also been observed in connection with DD. It was also found that individuals with DD have an elevated risk of being diagnosed with Type 1 Diabetes, and show an increased risk of heart failure which should be taken into account in patient management. [12] Thus, the purpose of this literature review is to explore the molecular pathogenesis of DD, investigate the various complications associated with DD, and to elucidate the degree to which these complications are observed in patients suffering from DD.

RESULTS

Molecular Pathogenesis of Keratosis Follicularis

DD is caused by genetic defects in ATP2A2 encoding the sarcoplasmic/endoplasmic reticulum Ca(2+)-ATPase isoform 2 (SERCA2). [13] SERCA2 is a calcium pump of the endoplasmic reticulum (ER) transporting Ca(2+) from the cytosol to the lumen of ER. ATP2A2 mutations lead to loss of Ca(2+) transport by SERCA2 resulting in decreased ER Ca(2+) concentration in Darier keratinocytes. [13] This eventually results in loss of cell-to-cell adhesion and abnormal keratinization. [13]

The alternative splicing of ATP2A2 gene gives rise to two isoforms of SERCA2 pump: SERCA2a, which is predominantly found in skeletal and cardiac muscles, and SERCA2b, which is found in all cell types but abundantly in smooth muscle cells. [14, 15] SERCA2b is different from SERCA2a by the presence of the “2b tail”. [16] It has been suggested that wildtype SERCA2b in keratinocytes exhibits high calcium affinity with the low transport rate, while mutations in SERCA2b lead to increased cytosolic calcium with the decreased peak calcium, and thus impairs the dynamic of calcium signaling. [16]

A high concentration of calcium inside of the ER is needed for the posttranslational processing of proteins that are destined to reach the plasma membrane. Depletion of calcium concentration in ER is associated with the accumulation of misfolded proteins in ER, which leads to initiation of stress response. [17] It has been shown that constant ER stress response leads to decreased adherens junction formations between the cells. [17] It has been also observed that loss of SERCA2b leads to formation of defective adherens junctions and desmosomes, which

results in diminished intercellular adhesion. [17] In other words, mutations in ATP2A2 that cause defective SERCA2b lead to low calcium concentration inside of ER, and thus impair proper processing of proteins that are responsible for cell-to-cell adhesion.

DD and Basal Cell Carcinoma

According to a variety of literature, an association has been found between DD and basal cell carcinoma (BCC). While no molecular link between DD and BCC has been established, the imbalance of cellular survival and apoptosis due to the DD mutation or other genodermatoses may contribute to the presence of BCC in individuals with DD. Darier's disease is caused by a loss-of-function mutation in the ATP2A2 that leads to a disruption of Ca2+homeostasis within the keratinocytes. A decreased SERCA activity leads to an upregulation of the transient receptor potential canonical 1 Ca channel that increases cell proliferation and resistance to apoptosis. [18] Additionally, it has been demonstrated that patients with DD have reduced expression of the antiapoptotic proteins Bcl-2 and Bcl-XL, which may activate apoptosis and lead to increased cell turnover. [19] Although quite rare, cases of squamous cell carcinoma (SCC) have also been seen in patients with DD. Robertson and Sauder report that at least 7 cases of SCC have been observed in association with DD since 1981. [20] However, no association was determined between DD and melanoma, Merkel cell cancer or any other kind of skin cancer. More investigation needs to be done to establish a relationship between DD and cutaneous malignancies that are not NMSC. [20] Moreover, alteration of ATP2A2 gene has been reported in the development of various other human carcinomas including colon and lung cancers. [21]

DD and Cutaneous, Ocular & Mucosal Manifestations

Nail involvement in individuals suffering from DD is not uncommon, and is frequently characterized by red or white longitudinal bands of varying width ending in a pathognomonic notch at the free margin of the nail, and subungual hyperkeratosis. Usually, the nails are found to be very fragile and brittle. Mucosal membrane involvement may occur as white papules on the buccal mucosae, palate, and gingiva with a cobblestone appearance. [22] Being a predominantly dermatological disease, ocular manifestations are rare in keratosis follicularis. They can present as punctuate corneal epithelial defects (photophobia), asymptomatic opacities in periphery of cornea, bilateral corneal subepithelial infiltrations, corneal ulcerations, or conjunctival keratosis.[23-25] Patients with Darier's are also prone to recurrent herpes keratitis and episcleritis. [26] There have been rare reports of other abnormalities including cataracts, basal cell carcinoma, retinal detachment, and in some patients, typical retinitis pigmentosa and even horn-like growths along the lid margin. [27-29]

DD and Neuropsychiatric Conditions

It has been observed that DD is associated with multiple neuropsychiatric conditions, such as major depression, bipolar disorder, schizophrenia, and suicidal ideations. [30] It was found that individuals with DD have a higher chance of being diagnosed with bipolar disorder and schizophrenia (4.3 and 2.3 fold higher, respectively). [11] It is thought that the genetic variability within the ATP2A2 gene which causes DD confers susceptibility for bipolar disorder in some patients suffering from DD. [11] Another study, that analyzed the results of standardized neuropsychiatric tests of one hundred individuals diagnosed with DD, suggests that neuropsychiatric symptoms of DD are rather the result of

ATP2A2 gene mutation, than the psychological response of the individuals to the cutaneous manifestation of DD. [30] Even though multiple mutations of ATPA2A2 are linked to DD, only specific locations of ATP2A2 mutations are associated with neuropsychiatric symptoms. [31] This relationship can be explained by the pleomorphic effect of ATPA2A loss of function mutations. [32]

DD and Diabetes

The relationship between DD and diabetes has also been observed. In a study conducted by Cederlöf et al, it was found that individuals with DD had a higher risk of being diagnosed with type 1 diabetes (risk ratio, 1.74; 95% confidence interval, 1.13-2.69) than those having type 2 diabetes (risk ratio, 0.88; 95% confidence interval, 0.37-1.36). [12] Given that most individuals with DD have mutations in ATP2A2, it is possible that the increased risk of Type 1 Diabetes is associated with ATP2A2 mutations and SERCA2 dysfunction. [12] Moreover, in the recent cross-sectional clinical study of metabolic phenotype of DD, it has been found that DD patients have lower fasting glucose level and higher c-peptide and HOMA2-%beta compared to their matched control group. [33]

This indicates that DD patients have a higher secretory capacity of islet cells and a higher basal insulin level. The authors emphasize that increased basal insulin is associated with worse control of glucose, and with time, may lead to type 2 diabetes. [33] The relationship between glucose metabolism and DD may be due to the fact that among different SERCA isoforms, SERCA2b is most abundantly expressed in pancreatic beta-cells. [14] It has been shown that the loss of SERCA2b due to mutations in ATP2A2, as seen in individuals with DD, leads to secretory dysfunction, and defect in proliferation and survival of beta-cells. [34] Additionally, inhibition of SERCA2b in beta-cells leads to initiation of the stress response by ER that induces apoptosis. [35]

DD and Heart Disease

Furthermore, it has been hypothesized that DD may be associated with heart diseases. This observation also strengthens the clinical evidence of the important role of SERCA2 in heart failure pathophysiology. [36] For example, even though patients with DD present with a normal clinical heart phenotype, they have a 59% higher chance of being diagnosed with heart failure compared to those without DD. [36] Interestingly, the loss of the ATPA2A allele by itself does not affect cardiac performance, however, the development of heart conditions may be worsened in patients with ATPA2A mutation. [37]

CONCLUSION

It can be concluded that DD is a multisystem rare autosomal dominant disorder that occurs typically in the first or second decade of life, and goes beyond involving the skin. While neuropsychiatric manifestations, diabetes mellitus type 1 and heart diseases are more commonly observed, rare instances of mucosal, nail and ocular changes have also been reported to occur in association with DD. Since UV light exposure exacerbates the condition, we recommend individuals with DD to avoid direct sunlight and apply sunscreen when going out. Furthermore, mild to moderate DD management includes the use of oral and topical retinoid as well as naltrexone. Dermabrasion and carbon dioxide or YAG laser are reserved for severe and refractory cases. It is crucial for dermatologists to anticipate and discern the extracutaneous manifestations associated with DD in order to be able to provide a timely and appropriate referral to other specialists,

including psychiatrists, endocrinologists and cardiologists, for further management.

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Corresponding Author:
Hira Ghani, BA
259 Palsa Avenue
Elmwood Park, NJ 07407
Phone: 201-925-5165
E-mail: hghani01@nyit.edu

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