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Darier's Disease: A Comprehensive Review of Literature

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ABSTRACT

Darier-White disease is known as keratosis follicularis as well, is an autosomal dominant inherited keratinization disorder that affects the skin, nails, and mucosal membranes. This disease has a chronic and usually recalcitrant treatment challenging course also has a great impact on patients' quality of life. In this comprehensive review article, we searched the most recent and related articles related to our topics and subtopics with emphasis on epidemiology and etiology, clinical symptoms, genetic changes and molecular pathogenesis, diagnosis and differential diagnosis, treatments and management also possible associations.

KEYWORDS

Darier's Disease, Darier-White Disease, Keratosis Follicularis, Keratinization, Clinic, Genetic, Diagnosis, Differential Diagnosis, Prognosis, Complications, Treatment, Associations.

Introduction

Darier disease(DD) (Darier-White disease) is an autosomal dominant inherited keratinization disorder which is known as keratosis follicularis too that affects the skin, nails, and mucosal tissues [1, 2]. Darier disease at first reported in 1889. The prevalence ofDD is reported to range from 1 in 30,000 to 1 in 50,000 (overally 1 in 100,000) and the prevalence rate is similar betwwenboth sexes [3-6].

DD often develops in childhood and persists throughout adolescence which is clinically evident in young adults, causing small papules that mainly predelict to seborrheic area. Further, scales and crusts may gradually develop. DD may be associated with non cutaneous symptoms, for instance psychiatric symptoms, such as mental retardation, epilepsy or bipolar disease. Histologically, DD is characterized by acantolytic dyskeratosis that means corps ronds and grains as deyskeratosisplus acantholysis which will cause suprabasal cleavage [4].

Clinical Symptoms

Darier disease usually appears between ages 6 and 20, with a peak in puberty for most patients. Keratotic papules are the most common signs which are yellowish to brown, greasy appearance located in the seborrheic areas of the face, scalp, and chest [1, 7].

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DD papules are not always follicular and often get together to form a verrucous plaques with keratotic crusts. The lesions are often associated with itching and are malodor. In particular, papules developing at sites of friction (like axilla and groin) are prone tobe infected and become exagerated. Furthermore, complications such as maceration and secondary infection may result in a significant malodor complains[3, 8, 9]. Mechanical trauma, humidity, heat, ultraviolet B, and bacterial, fungal and viral infections are some factors associated with clinical severity of the disease. Pruritus is a common symptom [7, 10].

In addition to a keratotic surface and hyperkeratosis, punctate depressions on the palms and soles and acrokeratosisverruciformisof hoefon the backs of the hands and feet, may be observed. Fingernails and toenails may become fragile and weak along with nail abnormalities include longitudinal white or red lines, grooves and distinctive V-shaped notches on the distal ends of the nail plates However, not any hair-related abnormalities have been seen in cases of DD [1, 9, 11].

Mucous membrane involvement is not common, although small white papules and nodules could be seen in the oral mucosa, the esophagus, the vulva, and the rectum as granular orpapillary lesions [3, 9, 12].Parotid salivary glands may also be involved. In up to 30% of patients periductal fibrosis and ductal obstruction cause intermittent swellings [13]. Oral lesions are thought to have no malignant potential but one squamous cell carcinoma case has been reported in a patient with Darier disease [13-15].

DD may be accompanied by non-cutaneous symptoms such as psychiatric symptoms, epilepsy, major depression, bipolar disorder, schizophrenia, and learning difficulties and mental retardation and etcalso psychiatric patients may have more sever DD [1, 9, 16]. Localized cases are considered to be due to genetic mosaicism caused by mutations that occur during zygotic division [17]. A rash with macular or linear patterns in one part of the body, with a distribution similar to epidermal nevus are some of the symptoms as segmental forms of darier[18].

Genetic Changes and Molecular Pathogenesis

Genetic variations are involved in many types of disorders[19-23].In 1993 the gene associated with DD was mapped to chromosome 12q23– 24.1 by linkage analysis, the autosomal dominant inheritable characteristic of DD was not identified until then [24, 25]. ATP2A2 gene, which encodes the type 2 sarco(endo)-plasmic reticulum Ca2+-ATPase (SERCA2), as the causative gene for DD [26].

The ATP2A2 gene is alternatively linked to three variants —SERCA2a, SERCA2b, and SERCA2c. These isoforms have differential tissue distribution, with SERCA2b which is the major skin isoform [3, 27]. Alternative splicing of exon 20 produces SERCA2a (997 amino acids) and SERCA2b (1042 amino acids), the second one has an eleventh transmembrane domain and a tail that extends into the ER lumen [28]. SERCA2c is a splice variant resulting from the inclusion of a short intronic sequence that has been identified more recently which contains an in-frame stop codon between exons 20 and 21 of SERCA2a [29]. SERCA2b is the main isoform expressed in the epidermis on skin sections. SERCA2a is also expressed usually in cardiomyocytes and slow-twitch skeletal muscles, but they have also detected this in smooth muscle cells, pancreatic epithelial cells and in cerebellar Purkinje cells [30-32].

The mammalian epidermis is a highly specialized, highly organized, stratified squamous epithelium consisting of basal, spinous, granular and cornified cell layers. Each layer is defined by different morphological and biochemical characteristics and state of differentiation of the keratinocytes. Epidermal cells experience a complicated program of terminal differentiation from the basal layers to the cornified layers to show a protective skin barrier. For making this program get going it needs the matched expression of a large number of genes and tight cell-to-cell adhesion until epidermal cells enter in a desquamation process. It has been recognized for many years that extracellular calcium is crucial in epidermal differentiation and intra-epidermal cohesion [33-36].

A steady-state of the ER Ca2+ pool is important for post-translational modifications, protein sorting, and the protein-folding machinery, because the function of many ER chaperones depends on local Ca2+ changes within the ER. SERCA pumps perform the crucial function of replenishing the depleted ER Ca2+ stores so they constitute an integral component of the cellular Ca2+ homeostasis circuitry [37-39]. The possible role of Ca2+ in the growth and differentiation of both epithelial cells and keratinocytes is recognized [33, 40, 41].

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ATP2A2 gene mutations cause insufficient amounts of functional SERCA2 enzyme. Darier keratinocytes display depleted ER Ca2+ stores as a result of the loss of SERCA2 Ca2+ transport on Ca2+ homeostasis (Fig.1)[42, 43].

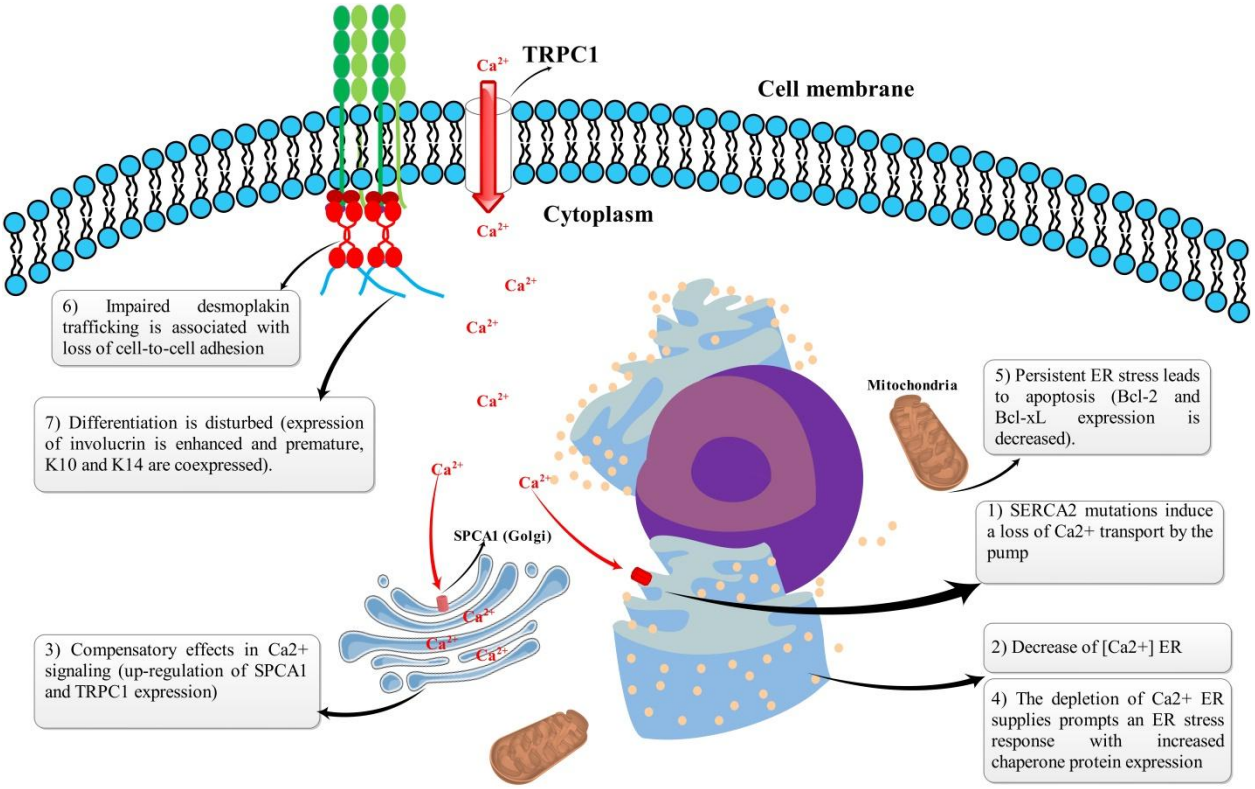

Figure 1. Subsequences of SERCA2 mutations in Darier keratinocytes. Steps in this picture (from 1 to 7) show the consequences of mutations in SERCA2 gene

As compared with the normal epidermis of healthy controls, the expression of Bcl-2 and Bcl-xL was obviously reduced in the lesional epidermis of the patients, but there was no change in expression of Bax (Fig1). The alterations in the expression of Bcl-2 gene family proteins could be a very important event for the activation of the apoptotic process in the lesional epidermis of DD patients and for the occurrence of the characteristic dyskeratotic keratinocytes [44].

Diagnosis and Differential Diagnosis

Although usually there are typical clinical presentations of Darier disease in predilection sites of skin, its appendageal and/or mucosa, but there are also many rare presentations such as localized-segmental/unilateral or bilateral linear or nevic forms of the disorder. The latter is about 10% of DD presentation and due to genetic mosaicisms like post-zygotic somatic- or gonadal mutations or loss of heterozygosity that leads to Blaschkoid- or widespread or more severe clinical presentation of the disease, respectively. So in the cases of linear or segmental lesions with differential diagnosis of linear psoriasis, linear lichen planus, verrucous epidermal nevus, lichen steriatus, we should consider segmental forms of DD, which is confirmed by skin biopsy and histopathologic examination [15], [45-50].

The more prevalent clinical differential diagnosis of Darier disease is acrokeratosisverruciformis of Hopf (with same mutation as DD), acanthosis nigricans, seborrheic dermatitis and confluent and reticulated papillomatosis of gougerot and carteaud. The more prevalent differential diagnosis of DD in pathology includes Hailey-Hailey, pemphigus vulgaris, or Grover disease [51, 52].

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There are many cases of missed or late diagnosis of DD. After clinical suspicion (recently dermatoscopy helps), confirmation of Darier disease is usually by histopathologic exam or in certain cases by genetic examination [53, 54].

Prognosis and Complications

Darier is a lifelong disorder with multiple courses of exacerbation. The disease usually triggers by excessive sweating, secondary infections, light exposure, heating, wearing heavy clothing and recurrent friction. This disease has a great impact on patients' quality of life regarding psychiatric problems (including cosmetic and malodorous concerns) [45, 51].

Due to abnormal keratinization leading to abnormal epidermal barrier in Darier or keratosis follicularis disorder, there are potential risks for infective cutaneous involvement, so that one of the most important complications of DD is superimposed; viral [55-57], bacterial [58] or fungal infections (Fig. 2) [59, 60] which even could be fatal (Fig. 2)[61-63]. It is proposed that patients with DD may have partial immunodeficiency or changes in cutaneous colonization [58, 64]. There are some reports of complications that are associated with treatment protocols like emerging of hemorrhagic lesions with systemic retinoids [65, 66].

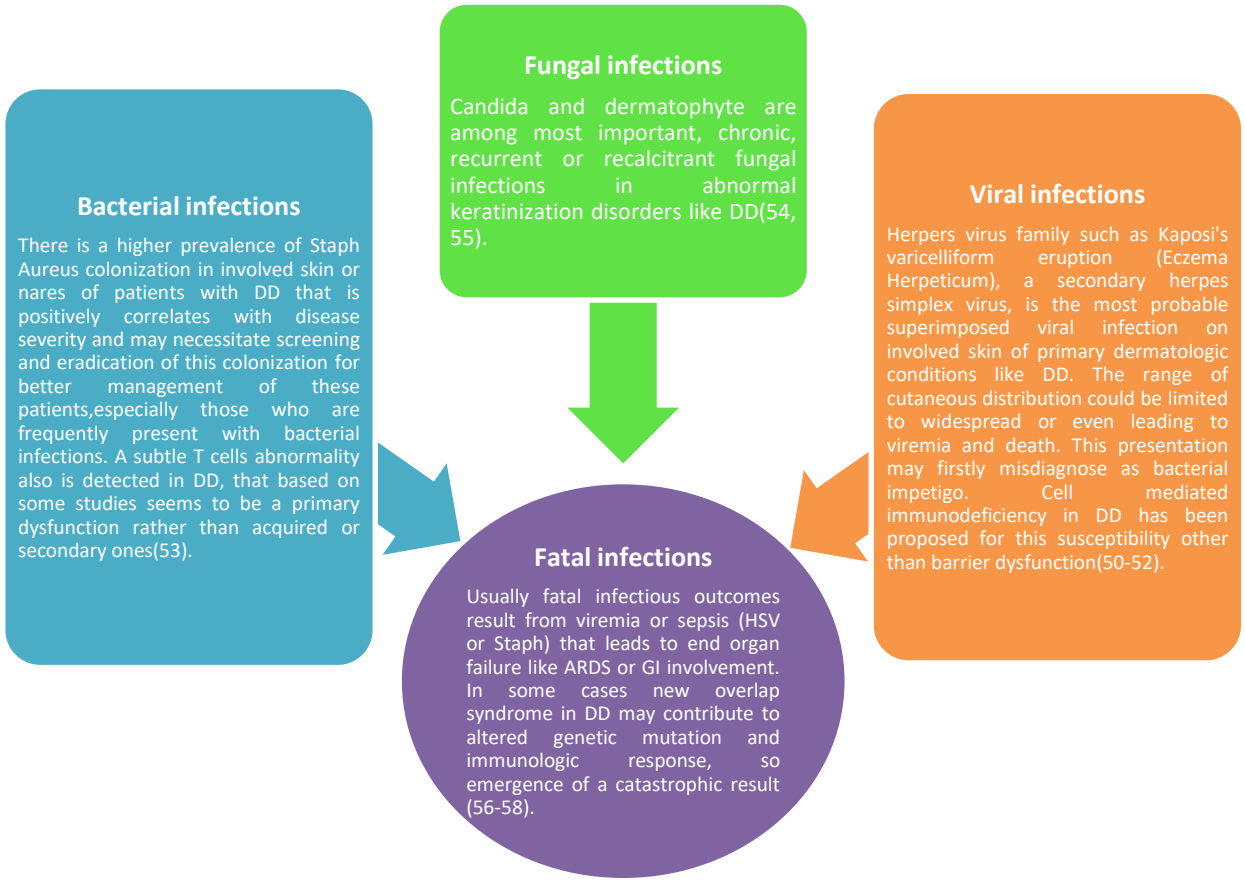

Figure 2. Potential risks for infective cutaneous involvement (Ref [55-63])

Treatment and Management

At first, patients should avoid mentioned triggering factors and regularly use an antiseptic solution for infection prophylaxis. Topical keratolytic moisturizers (like urea and lactic acid) and topical retinoids are usually enough for long term disease management[51],[9, 67-74]. There are many case reports and case series of using oral retinoids

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[75-80], 5-fluorouracil [81-84], light base therapies (lasers, photodynamic therapy, radiotherapy)[85-92], topical vitamin D analogues [69, 93], topical diclofenac gel 3% [94-96] and recently oral doxycyline or magnesium for treatment [97-99] of Darier disease (Table 1).

Table 1. Some of the treatment approaches and their features

Type of Treatment	Features	Ref
Topical retinoids	• Topical retinoids like Adapalene, Tazarotene, Tretinoin and Isotretinoin have been frequently used for treatment of DD. • Their response usually occurs in first 2 months of therapy and is higher than topical vitamin D analogues or topical urea. • Also short contact therapy about 6 weeks, have been proposed successfully with a long time lack of relapse especially about topical tazarotene.	[69, 70, 72, 100]
Oral retionoids	• Based on studies, acitretin and etretinate are both safe and effective in treatment of DD also it is needed about 4 months for showing disease clearance. • Alitretinoin also have been used in some studies for treatment of DD and has been shown significant decrease of symptoms after 1 week and clearance after 3 months of therapy with an acceptable safety profile and shorten contraception time after drug discontinuation which is really important to women in childbearing ages. • Isotretinoin also has been used in DD setting in a dosage of 20-40 mg/kg/day or (0.5-0.7 mg/kg/day) that if necessitates would be increased during 4-6 months and >50% symptomatic improvement within 2 weeks could be expected.	[75, 77-80]
5-fluorouracil	• In DD, mutations of the ATP2A2 gene that encoding SERCA2 endoplasmic reticulum calcium pumps leads to decreased ATP and calcium affinity also phosphorylation-dephosphorylation blockadge. With this knowledge 5-fluorouracil that results to restoration of normal intracytoplasmic calcium concentrations may normalize keratinization. • Topical 5-fluorouracil appears to an effective alternative for treatment of DD. • Alternate therapy of topical 5FU 1% and clobetasol has been shown significant improvement of DD during 5 months and 2months of sustain results after drug discontinuation with acceptable safety profile. • Significant therapeutic improvement may start in first few weeks and sustain for about 2-6 months after therapy. • Topical 5FU 1% have better responsibility comparing to 7.5% salicylic acid in petrolatum or 0.05% vitamin A acid cream. • In another study although initial success of topical 5FU 1%, the effect did not sustain during time and side effects appeared, so caution should be considered about its prolonged use. • It one study concurrent clinical use of oral alitretinoin and topical 5-FU leaded to a more durable clinically complete remission with a good tolerance rate.	[81, 82, 84]
Lasers	• Fractional CO2 laser and 1,550-nm erbium-doped fiber laser are among proposed lasers for treatment of DD. • These lasers with limited therapeutic sessions provide very good response without any permanent side effects like scars or pigmentary changes.	[85-87]

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Photodynamic therapy (PDT)	• PDT in combination with topical retinoids has been tried in a case series study as an effective and safe therapy comparative with systemic retinoids (treatment of choice for DD). • It is better to use PDT in combination with other therapeutic methods rather than the monotherapy especially in sever or recalcitrant cases who needed to b e manage in a systemic manner. • The therapeutic effect of PDT may sustain for months.	[88-90]
Radiotherapy	• Photon and electron beam radiation therapy may be used for treatment of DD in recalcitrant cases with long term improvement. • The positive effect of local radiotherapy in DD has been shown accidentally in a patient with breast cancer who underwent radiotherapy. • We should consider radiotherapy in sever and recalcitrant DD cases who needing long term sustainability of therapy, but dosage and proper technique requires prospective studies.	[91, 92]
Topical vitamin D analogue	• High-concentration tacalcitol lotion and sunscreen may be a good therapeutic option for DD.	[69, 93]
Topical diclofenac	• In few studies after 3-8 months of use of topical diclofenac sodium 3%, skin involvement of DD was significantly disappeared and sustained for acceptable time duration, with no adverse effects or any systemic absorption symptoms. • Similar effects related to COX enzyme pathway pathogenesis can be achieved by systemic use of the nonsteroidal anti-inflammatory drugs that need further investigations.	[94-96]
Oral doxycyline	• Recently proper therapeutic effects of doxycycline have been shown for Hailey-Hailey disease that has a similar pathogenic pathway to DD and because of its non-antibiotic properties (anti-inflammatory effects) and acceptable safety profile; it is comparable with systemic retinoids as a new and interesting DD treatment. • Doxycycline 100mg daily seems to have significant improvement results in DD. • Tetracyclines families both chelate and assist crossing of calcium from cell membranes that result in correction of the cellular calcium imbalances. • In addition, tetracyclines family inhibits metalloproteinase 9 that is significantly involved in DD pathogenesis. But further investigations are needed to more exact recommendations.	[97, 98]
Oral Magnesium	• The effect of $MgCl_2$ in Hailey-Hailey disease in in-vitro studies is decreasing the calcium efflux of target cells but not any effect on Golgi Ca^{2+} filling, which suggests a possible role in other similar pathogenic disorder like DD. • Use of oral magnesium chloride 300 mg daily has been proposed for treatment of DD. • After 4 weeks of therapy, the effect was appeared.	[99]

Possible Associations

There are many articles in literature that report probable psychological (bipolar, schizophrenia) [101-111], organ dysgenesia or failure (like GI and renal)[112-114], autoimmune disorder[115], myopathia[116], gynecomastia [117] and etc in DD. Especially there are proved evidence of similar genetic mutation for many psychological problems and mutated gene in DD.

Nowadays better management of genodermatoses is of great concerns and these days getting more knowledges about

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many aspects of dermatologic disorders especially probable associations and newest therapies of common dermatologic disorders[118-127]and proper therapeutic options of rare dermatologic disorders [128, 129]are of really great importance which we tried to discuss in this comprehensive review about DD.

Conclusion

Regarding recent progressive improvement toward different aspects of DD especially in new topics like therapies and associations, it is of great value to further future studies for better management of this disorder.

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Contributers

All the authors made extensive contributions to the final draft of this manuscript.

Conflict of Interests

We declare no competing interests.

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Ethical Approval

Not applicable.

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