Case Report

Darier disease: A rare genodermatosis

Hema Suryawanshi, Akshay Dhobley, Aparna Sharma[1], Pramod Kumar

Department of Oral Pathology and Microbiology, Chhattisgarh Dental College and Research Institute, Rajnandgaon, Chhattisgarh, [1]Department of Oral Pathology and Microbiology, Rajasthan Dental College and Hospital, Jaipur, Rajasthan, India

Abstract

Darier disease (DD), also known as keratosis follicularis or dyskeratosis follicularis, is a rare autosomal dominant genodermatosis with high penetrance and variable expressivity. It is caused by mutations of ATP2A2 gene which encodes the sarco/endoplasmic reticulum Ca^{2+} ATPase isoform 2. It is clinically manifested by hyperkeratotic papules primarily affecting seborrheic areas on the head, neck and thorax, with less frequent involvement of the oral mucosa. When oral manifestations are present, they primarily affect the palatal and alveolar mucosa, are usually asymptomatic and are discovered in routine dental examination. Histologically, the lesions show suprabasal clefts with acantholytic and dyskeratotic cells. We present a case of 35-year-old female patient with typical clinical and histological features of DD.

Keywords: Autosomal dominant, Darier disease, keratosis follicularis

Address for correspondence: Dr. Pramod Kumar, House No. 1, Shakti Nagar, Mal Godam Road, Etawah - 206 001, Uttar Pradesh, India.
E-mail: pramodsharma84@gmail.com
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INTRODUCTION

Darier disease (DD) or Darier–White disease, also known as keratosis follicularis, is an autosomal dominantly inherited genodermatosis characterized by greasy hyperkeratotic papules in seborrheic regions, nail abnormalities and mucous membrane changes.[1]

DD was initially described by Prince Marrow in 1886. The disease was first reported independently by Darier[2] and White[3] in 1889. White was first to recognize the genetic nature of keratosis follicularis (DD) by noticing that a mother and her daughter were affected. The first report of mucosal manifestations was described by Prindiville and Stern in 1917.[4]

It has high penetrance, variable expressivity and worldwide distribution. The onset of disease is in childhood and adolescence.[5,6] The prevalence of this disorder in the population is 1:100,000, mostly often affecting males,[7] thus indicating that the disease is a rare of its kind.

Clinically, the distinctive lesion is characterized by hyperkeratotic papules that coalesce into plaques and occur primarily not only in seborrheic but also in intertriginous areas.[8] Coalescence of the papules produces irregular warty plaques or papillomatous masses, which, in the flexures, become hypertrophic and malodorous with painful fissures. Associated abnormalities include nail abnormalities characterized by nail fragility, red and white longitudinal stripes and V-shaped notches at the free margin of the nails.[9] Secondary infection is common. Sun, heat and sweating exacerbate the disease. DD never remits, but oral retinoids may reduce hyperkeratosis. Neuropsychiatric abnormalities, including mild mental retardation and epilepsy, have been described in association with DD in

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a few families.[10] whether this is an association based on pleiotropism of the mutant gene or reflects coincidence is not clear.

The oral mucosa is affected in 50% of cases in these cases, lesions are usually asymptomatic and discovered during routine dental examination.[11,12] Lesions are represented by multiple firm papules with normal, whitish or reddish color, primarily affecting the palatal and alveolar mucosa. Initially, papules are reddish and may coalesce, forming crusts that may be ulcerated.[13,14]

DD is said to be caused due to mutations of ATP2A2 gene, which encodes the sarco/endoplasmic reticulum Ca^{2+} ATPase isoform 2 (SERCA2 protein).[13]

CASE REPORT

A 35-year-old female presented with eruptions on the body since the last 12–13 years with malodor from the same areas since 5–6 years and has been under herbal medication intermittently for the same but with no improvement. Eruptions were preceded by severe pruritus. There was no history of worsening or improvement of disease during pregnancy. The rash became itchy and infected during summer. There were no associated systemic complaints. The disease is progressive. Replace the sentence with this. Her parents and first-degree cousins were normal. Her 12-year-old daughter suffered from similar lesions, but parents or siblings were not affected by the same disease. The daughter did not accompany her mother in outpatient department.

The patient presented with greyish colored warty plaques scattered on the forehead, anterior scalp area [Figure 1], post- and pre-auricular areas, external ear, neck, nasolabial fold [Figure 2], dorsal surface of the hands [Figure 3], legs [Figure 4] and soles [Figure 5]. Characteristic V-shaped scalloping (nicking at the free margins) of the nails with longitudinal ridges parallel to the long axis were seen [Figure 6]. Nails at the distal ends were broken. Subungual keratosis was significant on the right hand. Crusted coalescing areas (plaques) were present on the dorsal surface of the hands and legs. Hyperkeratotic areas emanating malodor were present on plantar surfaces with similar nail changes in toes. Oral mucosa appeared to be normal. Anterior part of the scalp skin had discrete characteristic papules with rough and spiny surface.

Oral examination showed caries teeth, gingivitis and poor oral hygiene with absence of changes with respect to DD. No lesions were seen in other parts of the body. Blood counts, sugar, urea, creatinine and electrolytes were all normal.

Biopsy from the lesion was taken for microscopic examination and diagnosis.

Microscopic examination of the lesions shows hyperkeratosis along with central keratin plug. At places, the overlying epithelium shows acantholysis that results in formation of a suprabasilar cleft. In addition, the epithelial rete ridges associated with the lesions appear narrow and elongated. Examination of epithelium under higher magnification reveals varying numbers of dyskeratotic cells referred as corps ronds (round bodies) or grains (because of their resemblance to cereal grains). The underlying connective tissue is fibrocellular, composed of collagen fibers, fibroblasts, blood vessels and mild chronic inflammatory cell infiltrate [Figures 7-9].

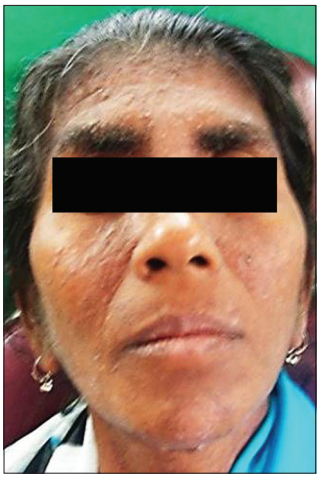

Figure 1: Presence of warty plaques on forehead and anterior scalp area

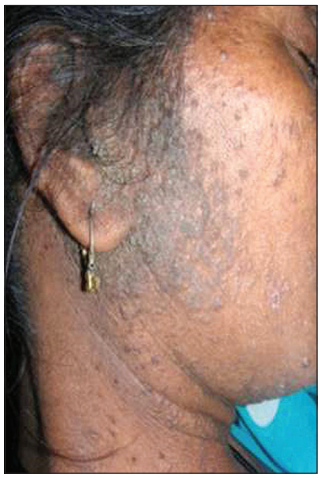

Figure 2: Hyperkeratotic papules and plaques on preauricular areas, external ear and neck

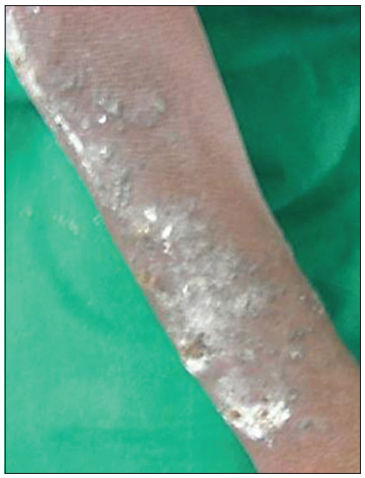

Figure 3: Hyperkeratotic plaques on dorsal surface of the hands

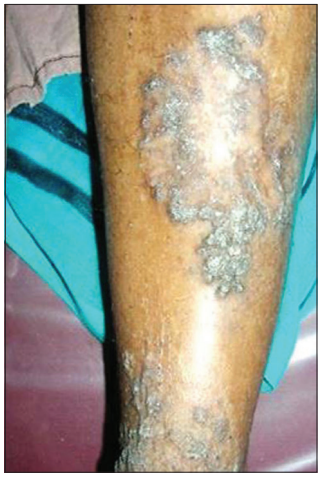

Figure 4: Hyperkeratotic plaques and papules on dorsal surface of legs

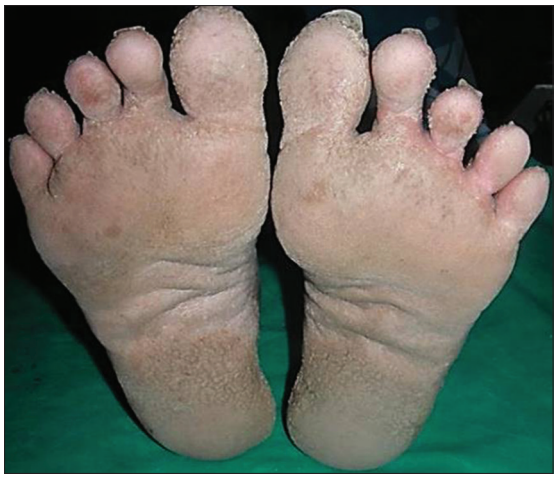

Figure 5: Hyperkeratosis on soles

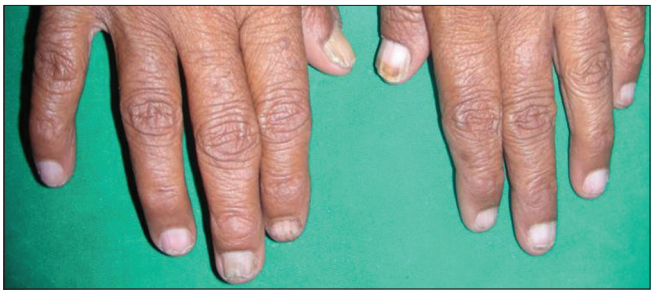

Figure 6: V-shaped notching seen on the right middle finger with longitudinal bands on nails

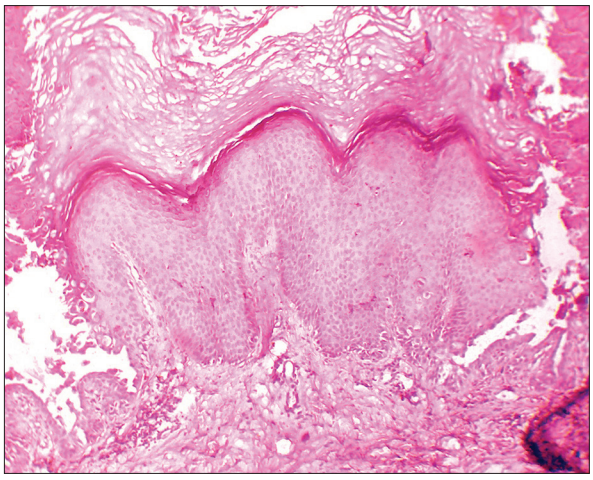

Figure 7: Photomicrograph showing hyperkeratosis, keratin plugging along with suprabasilar split (H & E stain, ×100 magnification)

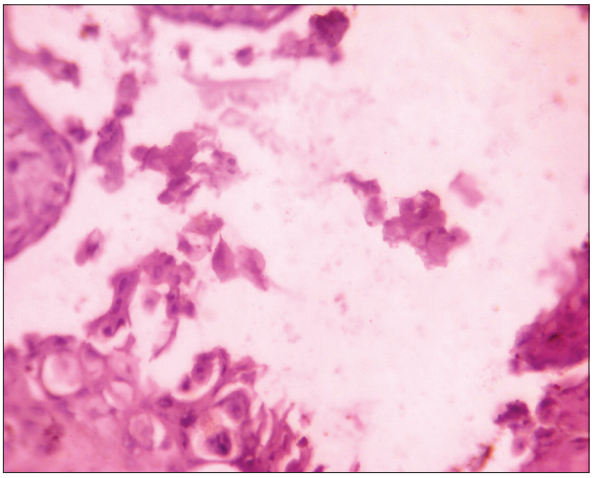

Figure 8: Photomicrograph showing dyskeratotic cells, i.e., corps ronds (round bodies) or grains (H & E stain, ×400 magnification)

DISCUSSION

DD is a rare keratinization disorder with skin involvement and relatively subtle oral mucosal lesions. It is characterized by hyperkeratotic papules in seborrhic regions and various nail abnormalities. DD is usually manifested during childhood or adolescence and has an equal gender distribution. Numerous erythematous pruritic small, firm papules appear first, later on become grayish brown, ulcerates and gets crusted. Foul odor may also be present as a result of secondary infection. Palmer and planter keratosis may be present with nail changes consisting of fissuring,

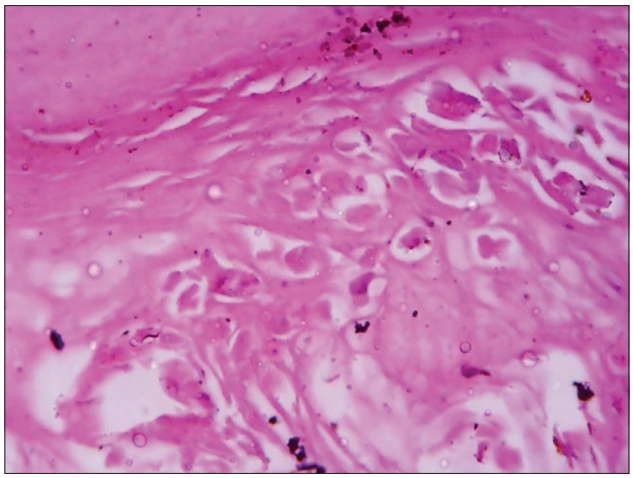

Figure 9: Photomicrograph showing dyskeratotic cells (H & E stain, ×400 magnification)

longitudinal streaking and subungual keratosis. On rare occasions, the clinical picture is dominated by skin fragility with painful erosions. Sunlight has been mentioned as an exacerbating factor. The frequency of oral lesions range from 15% to 50% and is present on the palate showing a cobblestone appearance.[14-16] The present case showed skin lesions and nail abnormality but with the absence of changes in oral mucosa.

There are three clinical variants of DD – (a) hypertrophic, (b) vesiculobullous (c) linear or zosteriform. Intraorally, moderate forms of the disease are similar to nicotine stomatitis and sometimes similar to inflammatory fibrous hyperplasia. Thus, smokers and denture wearers should undergo biopsy for final diagnosis. Acrokeratosis verruciformis of Hopf (who have dorsal hand lesions only) have been found to harbor mutations in ATP2A2, suggesting this condition may actually be a localized form of DD. Localized form of DD may have to be differentiated from epidermal nevi.[17]

The first attempts to identify the gene causing DD were made in 1992, when Munro *et al*.,[18] suggested a linking to chromosome 1q21-q22, where genes of "epidermal differentiated complex" are located. In 1993, Bashir *et al*.[19] and Craddock *et al*.[20] reported that they had mapped the gene to the long arm of chromosome 12 (12q), where keratin genes are located since the keratin genes are located closer to the centromere of chromosome 12 than to the region where DD has been mapped, keratin genes were excluded as candidates. Some authors have found that two isoforms of the ATP2A2 gene were expressed at high levels in cultured keratinocytes. The evidence of the mutatated ATP2A2 gene in DD patients confirmed involvement of this gene in the pathogenesis of the disease.

Thus, the disease is caused due to mutation in the gene ATP2A2, at chromosome 12q23-24.1.3 The gene encodes the SERCA type 2 protein (SERCA2), which is a calcium pump. SERCA2b, an isoform of SERCA2 is more widely expressed including epidermis. DD is caused by reduction in SERCA2b function leading to abnormal intracellular Ca^{2+} signaling and abnormal organization or maturation of complexes responsible for cell adhesion.[21]

Histologically, abnormal premature keratinization/ dyskeratosis, presence of cleavage, loss of epidermal adhesion (acantholysis), an upward proliferation of papillae into the clefts, presence of villi (elongated papillae, lined usually with only a single layer of basal cells), corps, ronds (keratinized cells with large basophilic nuclei) in the granular layer and grains are seen mostly in the horny layer. Lacunae are small suprabasal separations between epidermal cells (acantholysis) due to impaired desmosomes. The underlying dermal papillae, covered by a single layer of epithelium (stratum basale), project into these clefts and form villus-like structures. A large keratin plug, often showing focal parakeratosis, overlies each lesion. Hyperkeratosis is common. Electron microscopy reveals loss of desmosomes, breakdown of desmosomes keratin intermediate filament attachment and perinuclear aggregates of keratin intermediate filaments. There exists significant correlation between the clinical presentation of DD and intensity of histological features.[6,22] Thus, abnormal cell–cell adhesion and aberrant epidermal keratinization are the primary features of DD.

The differential diagnosis includes acne vulgaris, seborrheic dermatitis, acanthosis nigricans, confluent reticulate papillomatosis, prurigo pigmentosa and reticulate erythematomucinous syndrome. In acanthosis nigricans, lesions are more pigmented. In confluent reticulate papilomatosis the lesions are flat and confined to upper trunk. The harshness of papules on palpation helps to distinguish it from visually similar conditions such as prurigo pigmentosa and reticulate erythematomucinous syndrome. Histologically, the disease needs differentiation from benign familial pemphigus, Grover's disease and pemphigus vulgaris. Immunofluroscence of skin biopsy differentiate different acantholytic disorders.[6]

The implications of the DD are more associated with cosmetic and esthetic than functional implications since this is a benign dermatosis. However, depending on the severity of the disease and affected area, the patient has more complaints, and the emotional status may be damaged by esthetic reasons. The systemic treatment of the DD is symptomatic. The lesions relapses because of the

hereditary etiopathogenesis, especially in patients with the severe and generalized form of the disease, who are usually treated with systemic and topical retinoids and in whom oral lesions still persist.[23] In the present case, the patient gives history of similar lesions present with her 12-year-old daughter but in milder form. Both daughter and mother should undergo genetic counseling.

Milder forms respond to general measures such as improvement of hygiene, wearing cotton clothes, avoidance of heat, sunlight and use of sunscreens. Moisturizers containing urea and lactic acid, topical retinoids such as adapalene, tazarotene gel, 0.1% tretinoin can decrease scaling and hyperkeratosis. Antiseptic solutions such as triclosan or astringents are helpful. Topical 5-fluorouracil has also been used effectively. Injection boutolin toxin type A has also been used successfully for the relief of discomforting symptoms in one patient. Utilization of topical 1% Vitamin A acid is advocated in dyskeratoses, yet favorable outcomes have not been reported.[6]

In the oral cavity by utilization of nonalcoholic mouthrinses, since the coalescence of papules in skin or mucosa leads to accumulation of organic products (keratin degraded by bacteria), which causes a bad odor and favors the accumulation of microorganisms, producing secondary infection. Some authors mention that these complications are worsened by heat.[11]

Oral retinoids decrease hyperkeratosis, smoothen the papules and reduce odor. Oral antibiotics and acyclovir are often needed to suppress secondary bacterial and viral infections. Oral contraceptives help to reduce perimenstrual flares. Severe inflammatory exacerbations may respond to ciclosporin. Dermabrasion, electrosurgery, laser ablations of recalcitrant plaques with CO_2, ER: YAG, pulsed dye and 1550 ηm erbium doped fractional fiber laser have been successfully used. Photodynamic therapy with five aminolevulinic acid and surgical excision of hypertrophic intertriginous keratosis follicularis have also been reported.[24]

CONCLUSION

Regardless of the clinical severity and treatment option, the patient should receive genetic counseling with information on the inherited condition and risk of transmission to the offspring. A biopsy is fundamental in oral lesions to allow final diagnosis; based on this result; the patient should be referred to dermatological examination. Patients should be informed on the complications of this disorder and the care required. The emotional status in more severe cases should be followed by a psychologist; therefore, these patients should be treated by a multidisciplinary team.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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