Journal of Pakistan Association of Dermatologists 2011; **21 (4)**: 230-234.

Original Article

A clinical and histopathological study of Darier's disease

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Abstract

Background Darier's disease is an uncommon inherited skin disease transmitted in autosomal dominant pattern characterized by brownish keratotic papules particularly dense in the seborrheic areas of the body, palmar pits and nail dystrophy .The disease is often exacerbated by sun exposure, perspiration and heat.

Patients and methods
We selected 30 patients of Darier's disease from the dermatology OPD for the study. The histopathological examination was performed in all the patients.

Results Yellow brown crusted greasy papules were the commonest clinical feature seen in 100% patients, cobblestoning of palate was seen in 86.6% patients, palmar pits in 83.3% patients and keratotic papules were seen in 73.3% patients. Regarding the nail changes alternating red and white bands were seen in all the patients (100%) and V shaped nicking at the free margins of nails was seen in 93.3% patients. The histopathological features noted were hyperkeratosis (100%), suprabasal acantholysis (90%), acantholytic cells (86.6%) and corps ronds and grains (83.3%).

Conclusion Cutaneous changes, clinical and histopathological, in Darier's disease are similar to that described in the literature.

Key words
Darier's disease, keratosis follicularis, dyskeratosis.

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.[1,2] The disease was first reported independently by Darier and White in 1889. White was first to recognize the genetic nature of keratosis follicularis (Darier disease) by noticing that a mother and her daughter were affected.[3]

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Mutations in the gene ATP2A2 cause DD. ATP2A2, located on 12q23-24.1, encodes the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATP isoform 2 protein (SERCA2), which is a calcium pump.[4] This pump maintains a low cytoplasmic Ca^{2+} level by actively transporting calcium ions from the cytosol into the lumen of the endoplasmic reticulum. Although more than 113 familial and sporadic mutations in ATP2A2 have been identified in DD patients, attempts at genotype-phenotype correlation have not been successful.[5,6] Family members with confirmed identical ATP2A2 mutations can exhibit differences in the clinical severity of disease, suggesting that other genes or environmental factors affect the expression of DD. Abnormal keratinocyte-keratinocyte adhesion and aberrant epidermal keratinization are the primary histologic features of DD. Electron microscopy reveals loss of

desmosomes (epithelial intercellular junctions formed by membrane and submembrane protein complexes), breakdown of desmosome-keratin intermediate filament attachment, and perinuclear aggregates of keratin intermediate filaments.[7,8] The mechanism by which decreased activity of the SERCA2 calcium pump leads to these changes is still under investigation.

The study was undertaken to examine the epidemiology and clinical profile and histopathological characteristics of Darier's disease.

Patients and methods

30 patients of DD from the dermatology OPD were selected for the study. Written informed consent was taken from all the patients. Prior approval of hospital ethical committee was taken before the start of the study. Routine investigations of all the patients were performed before the study including complete blood count, fasting blood sugar, ESR, urine complete examination, liver function tests and kidney function tests. The histopathological examination was performed in all the patients. The clinical and histopathological characteristics were recorded on a pro forma. The data was tabulated and the results were analysed.

Results

The demographic and clinical data of patients is shown in **Table 1**. The commonest age group of patients was 11-20 years (50% patients). Males outnumbered females and male:female ratio was 2:1. Family history was positive in 53.3% patients. Yellow brown crusted greasy papules were the commonest clinical feature seen in 100% patients (**Figures 1** and **2**), cobblestoning of palate was seen in 86.6% patients, palmar pits in 83.3% patients (**Figure 3**) and keratotic papules were seen in 73.3% patients.

Table 1 Demographic and clinical characteristics of patients with Darier's disease (n=30)

Characteristic	*N (%)*
Age distribution (years)	
0-10	1 (3.3)
11- 20	15 (50)
21-30	10 (33.3)
31-40	2 (6.6)
41-50	1 (3.3)
51- 60	1 (3.3)
Sex	
Male	20 (66.7)
Female	10 (33.3)
Family history	
Positive	16 (53.3)
Negative	14 (46.6)
Clinical features	
Yellow brown crusted greasy papule	30 (100)
Palmar pits	25 (83.3)
Cobblestoning of palate	26 (86.6)
Keratotic papules	22 (73.3)
Nail changes	
Red and white bands	30 (100)
V-shaped nicking at free margin	28 (93.3)
Sites of involvement	
Trunk	30 (100)
Retroauricular region	28 (93.3)
Forehead	25 (83.3)
Inguinal region	21 (79)

Table 2 Histopathological changes in Darier's disease (n=30)

Sr. No	*Histopathological feature*	*N (%)*
1.	Hyperkeratosis	30 (100)
2.	Suprabasal acantholysis	27 (90)
3.	Corps ronds and grains	25 (83.3)
4.	Acantholytic cells	26 (86.6)
5.	Papillomatosis	18 (60)

Regarding the nail changes alternating red and white bands were seen in all the patients (100%) [**Figure 4**] and V-shaped nicking at the free margins of nails was seen in 93.3% patients. Trunk was the commonest site of involvement seen in 100% patients, followed by retroauricular region in 93.3%, forehead in 83.3% and inguinal region in 70% patients.

None of the patients had any neuropsychiatric symptoms.

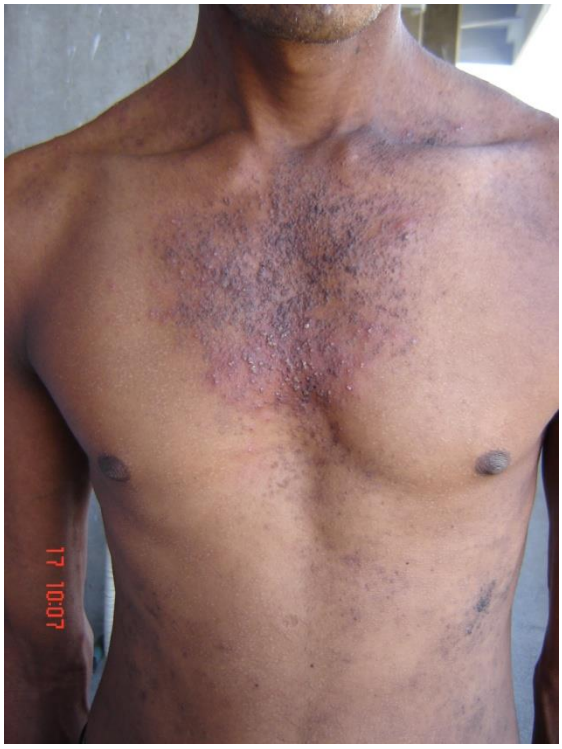

Figure 1 Greasy papules on the trunk in a 40-year-old male.

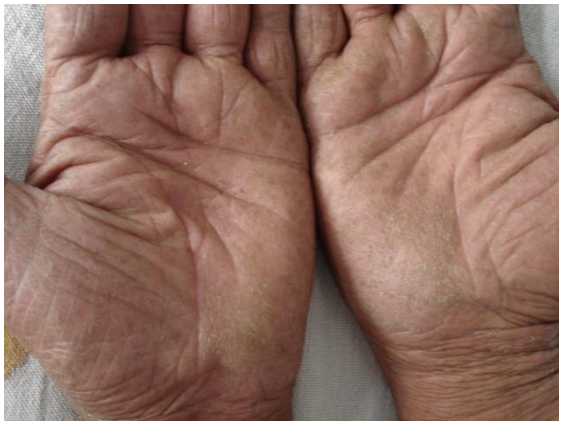

Figure 3 Palmar pits.

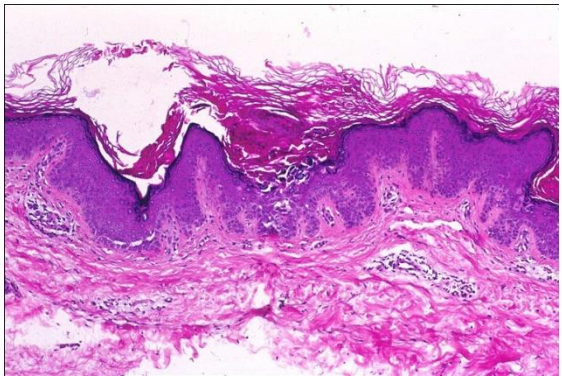

Figure 5 Photomicrograph of Darier's disease showing hyperkeratosis, suprabasal acantholysis and dyskeratotic cells (H&E stain 100X).

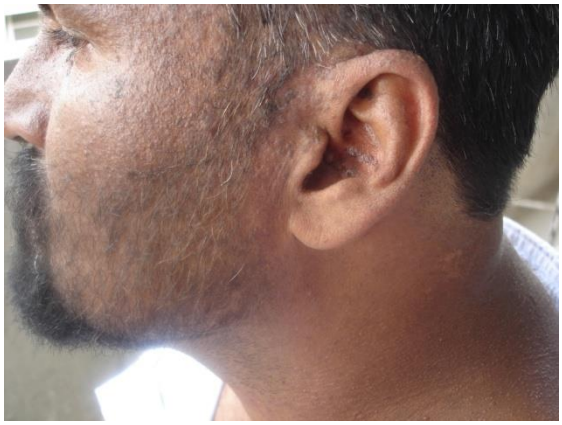

Figure 2 Yellow-brown crusted greasy papules in and around ears.

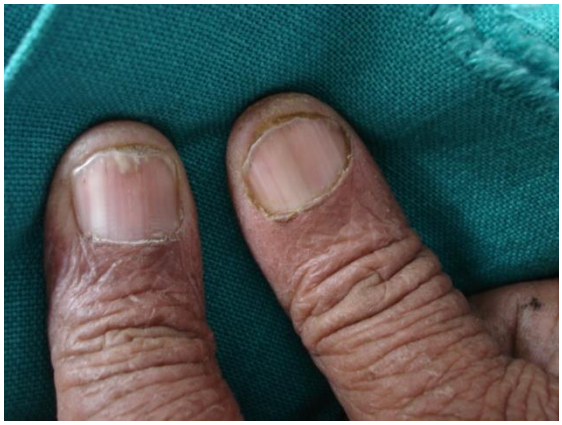

Figure 4 Nails showing triangular red and white bands.

Table 2 shows the histopathological changes seen. The commonest histopathological feature was hyperkeratosis seen in 100% patients, suprabasal acantholysis was seen in 90% patients, acantholytic cells were seen in 86.6% patients and corps ronds and grains were seen in 83.3% patients.

Discussion

In our study, the commonest age group of patients was 11-20 years (50% patients), 33.3% patients were between 21-30 years; 6.6% patients were between 31-40 years and 3.3% patients were between 41-50 years, 51-60 years and 0-10 years each. The male: female ratio was 2:1. Positive family history was seen in 53.3% patients. Our results in terms of age of onset and sex distribution are similar to the previous data.

Yellow brown crusted greasy papules were the commonest clinical feature seen in 100% patients, cobble stoning of palate was seen in 86.6% patients, and palmar pits in 83.3% patients and keratotic papules were seen in 73.3% patients. Regarding the nail changes alternating red and white bands were seen in all the patients (100%) and V-shaped nicking at the free margins of nails was seen in 93.3% patients. The trunk was the commonest site of involvement seen in 100% patients, retroauricular region was involved in 93.3% patients, forehead involvement was seen in 83.3% patients and inguinal region was involved in 70% patients.

The commonest histopathological feature was hyperkeratosis seen in 100% patients, suprabasal acantholysis was seen in 90% patients, acantholytic cells were seen in 86.6% patients and corps, ronds and grains were seen in 83.3% patients. These results are consistent with previous studies.[9-12]

DD most commonly manifests from age of 6 to 20 years; however, patients have presented as early as age 4 years and as late as age 70 years.[9] Notably, the first case of congenital DD was diagnosed by histopathology in a child with a significant positive family history for DD, in which at least the 3 preceding generations were affected.[10] Most patients with DD have a family history of the disease. The pattern of inheritance is autosomal dominant. However, some patients, up to 47% in one series, had no clear family history. These cases may represent sporadic mutations, or may have family members with mild disease who were not recognized.[11]

The first skin lesions typically occur in the teenage and are frequently associated with pruritus. Heat, sweat, humidity, sunlight, UVB exposure, lithium, oral corticosteroids, and mechanical trauma have been reported to exacerbate this condition. Some females report flares around menstruation. Even though the severity of the disease fluctuates over time, DD is a chronic, unremitting condition. In one study, one third of patients noted improvement with age; however, another one third of patients showed worsening of the disease with age.[2,12] Although neuropsychiatric abnormalities such as epilepsy, mental impairment, and mood disorders have been associated with DD, no evidence indicates that mutations in *ATP2A2* are associated with these disorders. One study suggested that a susceptibility locus for bipolar disorder co-segregates with DD region, but it is distinct from mutations causing DD.

The lesions may first appear as skin-colored or yellow-brown papules with a greasy, warty texture. These lesions are especially common in seborrheic areas such as the forehead, scalp, margin of the scalp, nasolabial folds, ears, chest, and back. Approximately 80% of patients have mild flexural involvement with scattered papules in the groin, axillae, or, in women, submammary skin. In less than 10% of patients, flexural disease predominates, with large, warty, vegetative plaques in the axillae, groin, or perineum. These large flexural lesions are especially bothersome to patients because of their malodor.[13] Involvement of the hands is very common (approximately 95%). Lesions on the palms include punctate keratoses (80%), palmar pits (80%), and hemorrhagic macules (<10%). Acrokeratosis verruciformis-like lesions (warty flat-topped papules on the dorsal hands) are present in approximately half the patients. Interestingly, several patients with 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.

Nail changes provide important diagnostic clues. White and red longitudinal bands,

longitudinal nail ridges, longitudinal splitting, and subungual hyperkeratosis are frequently found. A sandwich of red and white longitudinal bands, often with a V-shaped nick at the free margin of the nail, is the most pathognomonic nail finding in patients with DD.[14] These changes on the hands can also occur on the feet, albeit less commonly. Mucosal lesions are detected in approximately 15% of patients, and these appear as white papules with a central depression. These cobblestone lesions are most commonly found in the mouth, but they also may occur on the anogenital mucosa. At times, oral lesions may affect the salivary glands and cause obstruction.[15] Clinical variants of DD include hypertrophic and vesicobullous types.[16] Linear or segmental keratosis follicularis (Darier disease) has been shown in some cases to result from genetic mosaicism of ATP2A2.

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