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HISTOPATHOLOGICAL STUDY AND CLINICAL PRESENTATION OF DARIER'S DISEASE

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Abstract:

Darier's disease is infrequent, inherited autosomal dominant disease of the skin categorised by intense brownish keratotic papules in the palmar fossa, nail dystrophy and seborrheic parts of the body. The disease is usually aggravated by the exposure to sunlight, heat and sweating.

Aim: *The purpose of this analysis was to determine the clinical profile, epidemiology and Darier's disease histopathological characteristics.*

Study Design: *An Observational Study.*

Place and Duration: *In the dermatology outpatient department of Pakistan Institute of Medical Sciences (PIMS), Islamabad for one year duration from March 2018 to March 2019.*

Methods: *Thirty Darier's disease patients from the OPD of dermatology selected for the study. In all subjects; analysis of histopathology was done.*

Results: *The usual clinical feature seen in almost every patients were Yellow brown crusted greasy papules and in 86.6% of patient's cobble-stoning of palate was seen, in 73.3% of the cases have keratotic papules and palmar pits in 83.3% of the subjects. In all subjects, Alternative white and red bands were seen and V-shaped notches were found on the free edges of the nails in 95.3%. The observed histopathological characteristics were suprabasal acantholysis (90%), hyperkeratosis (100%), grains and corps ronds (83.3% and acantholytic cells (86.6%).*

Conclusion: *Cutaneous, histopathological and clinical changes in Darier's disease are same to those defined in the prose.*

Keywords: *Dyskeratosis, keratosis follicularis, Darier's disease.*

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INTRODUCTION:

The follicular keratosis is the other name of Darier disease (DD), is an autosomal dominant hereditary genodermatosis categorized by nail abnormalities, changes in the mucous membranes and sebaceous hyperkeratotic papules[1-3]. In 1889 by White and Darier White; the disease was first reported independently and he was the first person to identify the follicular keratosis (Darier's disease) genetic structure by observing that a daughter and mother were affected[4-5].

Darier disease is caused due to ATP2A2 gene mutations. The ATP2A2 of 12q23-24.1 encrypts the endoplasmic/ sarcoplasmic reticulum Ca2 + -ATP protein isoform 2 (SERCA2), a calcium pump. This pump help in maintaining cytoplasmic Ca2 + low level by calcium ions active transport from the cytosol to the endoplasmic reticulum in its lumen[6]. Though above 113 sporadic and familial ATP2A2 mutations have been recognised in patients with DD, phenotype- genotype correlation attempts have failed. Family members with the same ATP2A2 mutations detected may vary in severity clinically of the disease, indicating that other environmental or genetically factors alter DD expression[7]. The abnormal epidermal keratinization and abnormal keratinocyte-keratinocyte adhesion are the main DD histological features[8]. Electron microscopy shows the desmosomes loss (lower membrane protein complexes and inter epithelial intercellular junctions made by membrane), intermediate filament desmosome-keratin attachment separation and the perinuclear aggregates junction of the intermediate keratin filaments[9]. The study was performed to investigate clinical profile, histopathological features and epidemiology of Darier's disease.

MATERIALS AND METHODS:

Thirty DD subjects were selected for the study from the OPD of dermatology of Pakistan Institute of Medical Sciences (PIMS), Islamabad for one-year duration from March 2018 to March 2019. From all patients; informed consent in written form was taken. Prior to the study, approval was obtained from the hospital ethics committee. Routine examinations of all patients comprising fasting blood glucose, complete blood count, full urine test, ESR, renal function and liver function tests were performed. In all subjects; Histopathological examination was done. On Performa, histopathological and Clinical topographies were recorded. The results were analysed and data was tabulated.

RESULTS:

In Table 1, clinical and Demographic data of the patients are given. 11-20 years (50%) was the patient's most common age group. The 2: 1 was M: F ratio. In 53.3% of subjects, the family history was positive. The usual clinical feature seen in almost every patients were Yellow brown crusted greasy, in 86.6% of patient's cobble-stoning of palate was seen, in 73.3% of the cases have keratotic papules and palmar pits in 83.3% of the subjects. In all subjects, Alternative white and red bands were seen and V-shaped notches were found on the free edges of the nails in 95.3% as given in figure 1, 2, 3 and 4.

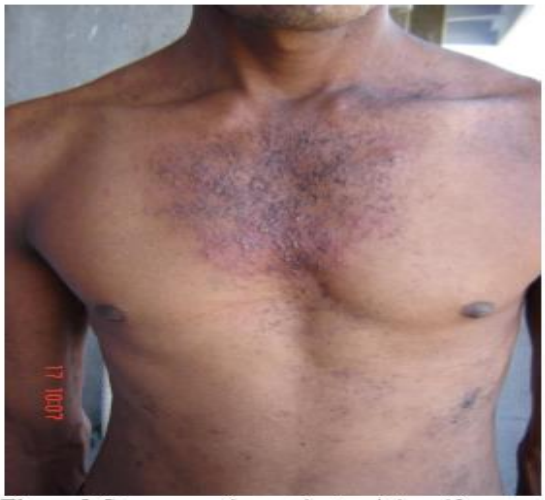

Figure 1 Greasy papules on the trunk in a 40-year-old male.

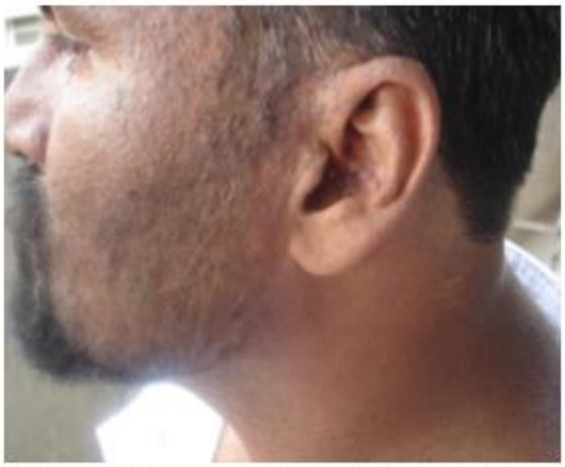

Figure 2 Yellow-brown crusted greasy papules in and around ears.

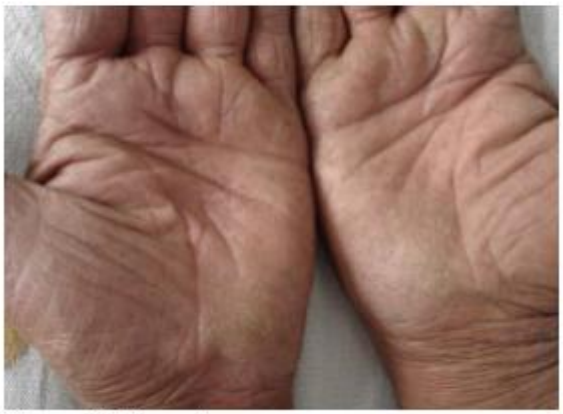

Figure 3 Palmar pits.

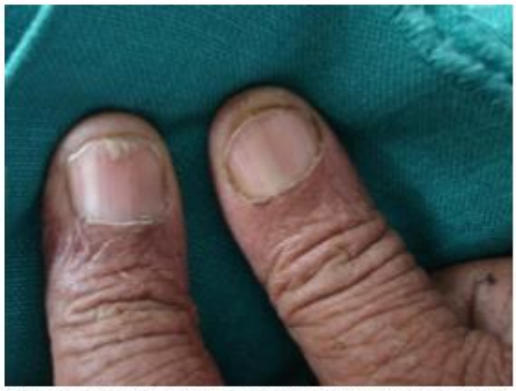

Figure 4 Nails showing triangular red and white bands.

In all subjects, the trunk was the most common involvement sit followed by the forehead in 83.3%, in 93.3% the retroauricular region was involved, and in 70% the inguinal region was involved.

The clinical characteristics and demographic data of Darier's disease patients (n=30).

Patients age in years and Characteristics	Percentage N (%)
One to yen years(0-10)	One (3.3)%
Eleven to Twenty years(11- 20)	Fifteen (50)%
Twenty one to Thirty years(21-30)	Ten (33.3)%
Thirty one to forty years(31-40)	Two (6.6)%
Forty one to Fifty years(41-50)	One (3.3)%
Fifty one to Sixty years(51- 60)	One (3.3)%
Sex	
Women Ten (33.3)%	Men Twenty (66.7)%
Family History	
Negative in 14 (46.6)%	Positive in 16 (53.3)%
Clinical characteristics	
Keratotic papules in 22 (73.3)%	Cobblestoning of palate in 26 (86.6)%
Palmar pits in 25 (83.3)	Yellow brown crusted greasy papule in 30 (100)
Nail changes	
Red and white bands in 30 (100)%	V-shaped nicking at free margin In 28 (93.3)%
Involvement site	
Trunk 30 (100)%	Inguinal region 21 (79)%
Forehead 25 (83.3)%	Retroauricular region 28 (93.3)%

The neuropsychiatric symptoms were not found in any patient. The observed histopathological features are given in Table 2.

The Darier's disease Histopathological features are given in Table II

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

The observed histopathological characteristics were suprabasal acantholysis (90%), hyperkeratosis (100%), grains and corps ronds (83.3% and acantholytic cells (86.6%).

DISCUSSION:

11-20 years (50%) was the patient's most common age group (50% of patients), 21 and 30 years patients were 33.3%, between 31-40 years, there were 6.6% patients and 41-50, 51-60 and 0-10 years patients were 3.3%, years[10-11]. The 2: 1 was M: F ratio. In 53.3% of subjects, the family history was positive. Our results are similar to previous data in terms of sex and age dispersal[12]. Our study results are comparable with earlier analysis. DD is usually seen between 6 and 20 years of age; however, patients presented in as short as 4 years and 70 years. In particular, the first inherited DD case was spotted in a child by histopathology with at least 3 generations of history affected, having a positive family history for DD[13]. The autosomal dominance is the heredity pattern. The family history was positive in those patients. Though, few individuals did not have a clear family history of up to 47% in a series[13]. The sporadic mutations was observed in these cases or have relatives with disease in mild form that are not documented.

The 1st lesions of skin occurs typically during puberty and are often accompanied with itching. Sweat, heat, sunlight, UVB rays exposure, moisture, oral corticosteroids and lithium were testified to aggravate the situation. Some women have reported outbreaks around menstruation. Although the disease severity varies with time. DD is a persistent and chronic condition. In this analysis, 1/3rd of subjects had an improvement as time passes; however with age, disease worsened in 1/3rd of cases. Though neuropsychiatric anomalies such as mental disorder, mood disorders and epilepsy have been related with Darier disease, there is no confirmation to suggest that ATP2A2 mutations are linked with these anomalies. The lesions may seem yellowish brown with papules of skin-colour or oily and warty tissue. In seborrheic areas, these type of lesions are common particularly seen in areas such as the scalp, nasolabial folds, chest, back, forehead and ears. 80% patients approximately have mild participation with papules scattered in the armpits, underarm skin or groin area in women. The flexural disease predominates in below 10% of subjects with warty and vegetative plaques in the perineum, armpits or groin[14]. For patients, large flexural lesions are worrying due to their bad smell. In 95% approximately, there were hands involvement. Palm lesions include palmar holes and punctate keratoses in 80% and <10% haemorrhagic macules. Lesions similar to verruciform acrokeratosis (dorsal hands lesions) were observed in 50% of the cases. Stimulatingly, many individuals with acrokeratosis verruciform (only dorsal hand lesions) were noted to ATP2A2 harbor mutations, signifying that this result in localized Darier disease. The changes in nails offer significant analytic tips. Often there are red and white bands seen as longitudinal phase, subungual hyperkeratosis and longitudinal division. A sandwich consisting of red and white bands in longitudinal phase, usually the nail free edge with a V-shaped notch, is the utmost pathognomonic nail verdicts in Darier disease patients. In the feet, these changes were also noted[14]. Although, it is least common. In 15% patients approximately, mucosal lesions are seen and are seen as white papules with depression in the centre. In the mouth, cobblestone lesions are usually seen but in anogenital mucosa was also seen. Infrequently, oral lesions can cause obstruction and affect the salivary glands. The DD clinical variables include vesicobular and hypertrophic types. In some cases, segmental or linear follicular keratosis (Darier's disease) has been demonstrated ATP2A2 genetic mosaicity.

CONCLUSION:

Cutaneous, histopathological and clinical changes in Darier's disease are same to those defined in the prose.

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