CASE REPORT

CLASSICAL PRESENTATION OF DARIER'S DISEASE: A RARE DISORDER OF KERATINISATION

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Keratosis follicularis or Darier's disease (DD), a rare autosomal dominant disorder is characterised clinically by appearance of multiple, prurutic, discrete, scaly papules affecting seborrheic areas coupled with palmar pits, nail changes and mucosal involvement. Histologicaly the lesions show suprabasal clefts with acantholytic and dyskeratotic cells. We report a case of 35 years old woman with typical clinical and histological features of Darier's disease.

Keywords: Autosomal dominant, palmar pits, suprabasal clefts, Darier's disease

INTRODUCTION

Darier's disease (DD), initially described by Prince Marrow in 1886 and by Darier and White in 1889[1] has high penetrance, variable expressivity[2] and worldwide distribution[3]. The onset of disease is in childhood and adolenscence.[2] Both sexes are equally affected.[4] The clinical features include hyperkeratotic, waxy papules, skin coloured plaques or minute acanthomas on front of chest, retroauricular areas and central T zone of face. The nail changes show short and wide nails, white and red longitudinal bands, V-shaped notch and scalloping of distal nail plate and subungual hyperkeratosis.[3] The palmar pits are pathogonomic.[3] Mucus membranes may show asymptomatic papules with central depression or cobblestone papules on palatal and alveolar mucosa in 50% of cases.[1] Plane wart-like lesions on dorsa of hands and feet and guttate leukoderma may be early features of disease.[3] However there is great variability in extent of involvement ranging from typical nail changes only to generalized disease.[5] The disease persists throughout life, runs a chronic relapsing course, without affecting general health.[3] Exacerbations have been reported by heat, sunlight, UVB, lithium, oral corticosteroids,[3] mechanical trauma and menstruation.[4] Variable presentations like nevoid, vesiculobullous, flexural erosive or hyperkeratotic, hemorrhagic macules, comedones or nodulocystic acne,[3] congenital[6] and paraneoplastic variants[7] are reported. Neuropsychiatric associations[3] and fatal bacterial and viral infections have been described.[8]

Histology shows dyskeratosis in spinous layer (corps ronds) and stratum corneum (grains), suprabasal acantholysis and clefts (lacunae). 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.[3,4]

CASE REPORT

A 35 years old female presented in Dermatology OPD, SZH with papules on seborrhoeic sites, dorsa of hands and feet, diffuse hair fall and hyper and hypopigmented lesions on limbs and back. The rash became itchy and infected during summer, especially while working in kitchen. Illness started in her teens with papules on the dorsa of hands and feet. There was no history of worsening or improvement of disease during pregnancy. There were no associated systemic complaints. Since then the disease is progressive. Her parents and first degree cousins and normal. None of the 8 siblings are affected. Her husband is her first cousin, he and two children are normal.

Examination revealed multiple reddish brown, discrete, scaly, rough papules on chest, sub-mammary region, (Figure-1) retoauricular areas, (Figure-2) sides of neck and plane topped papules on dorsa of hands and feet (Figure-3). Hypo and hyperpigmented macules and plane topped papules were distributed on the back, upper and lower limbs (Figure-4). Her face had hyperpigmentation more pronounced around eyes, forehead, perioral area and nasolabial folds. Axillae, antecubital fossae, groins and popliteal fossae also had mild hyperpigmentation. Palms had yellowish, puntate keratosis with pits (Figure-5). All nails showed light and dark longitudinal bands. Distal nail plate splitting, scalloping and V-shaped notch was present in one of the nails (Figure-6). She had diffuse scalp hair loss. The hair was short, dry and lustreless. Scalp skin had discrete characteristic papules with rough and spiny surface. Oral examination showed caries teeth, gingivitis and few small, discrete, asymptomatic reddish papules on hard palate mucosa. Examination of genitals was unremarkable. Blood counts, sugar, urea, creatinine and electrolytes were all normal.

Skin biopsy from right retro auricular area and infra-mammary region showed focal suprabasal clefts with acantholytic cells, corps ronds in stratum malpighii, grains in stratum corneum and dermal mild chronic inflammatory cells infiltrate. No granuloma or malignant cells were seen (Figure-7, 8).

She was put on oral antibiotic, topical 2% urea cream along with advice to improve general hygiene,

wearing of cotton clothes and avoidance of heat and sunlight. As she had not completed her family so the option of oral retinoids was not considered.

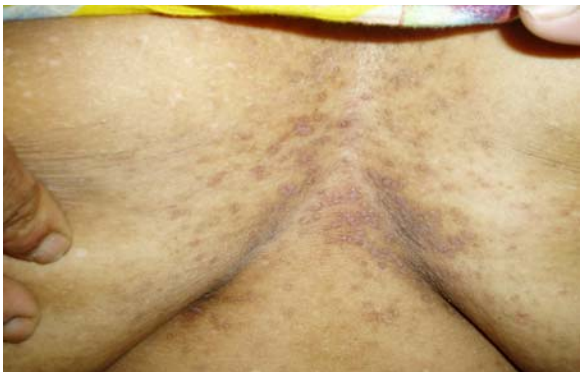

Figure-1: Erythematous, discrete, scaly papules on chest and inframammary area

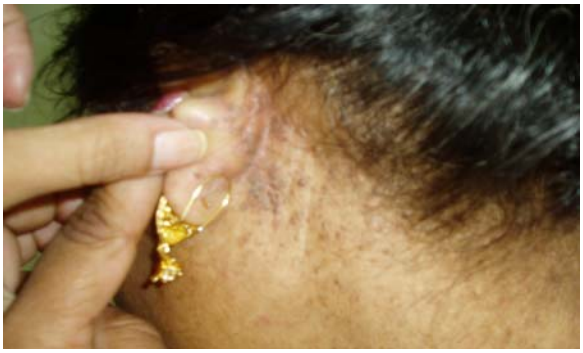

Figure-2: Discrete, Erythematous and hyperkeratotic papules in retoauricular area and also extending into scalp

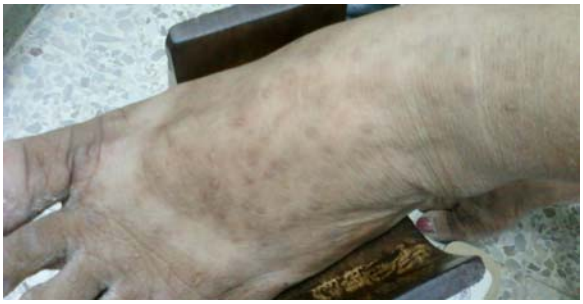

Figure-3: Plane topped papules on dorsum of foot

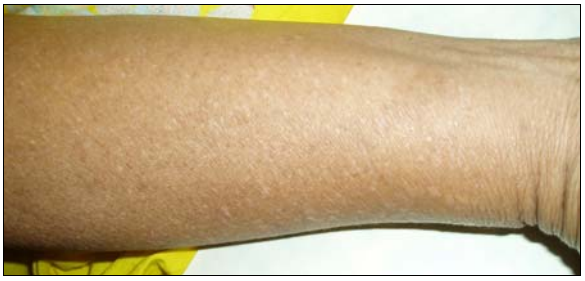

Figure-4: Guttate leucoderma and hyperpigmented macules and papules on arm

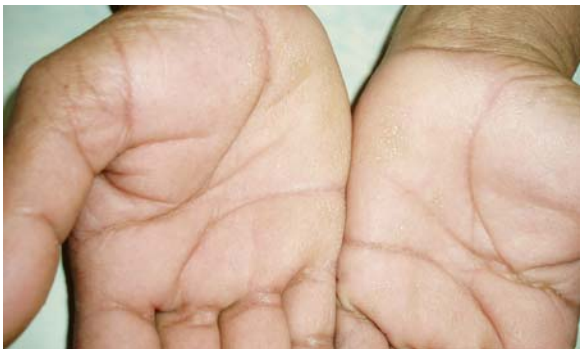

Figure-5: Pathogonomic palmer pits

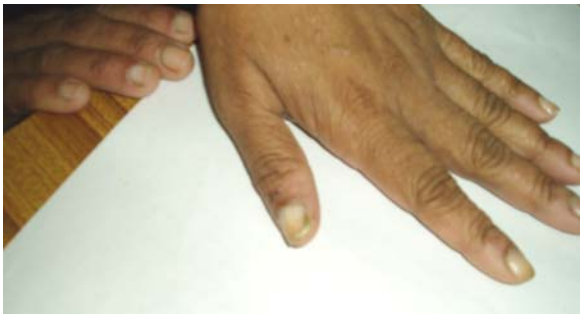

Figure-6: Distal nail of thumb showing V-shaped notch

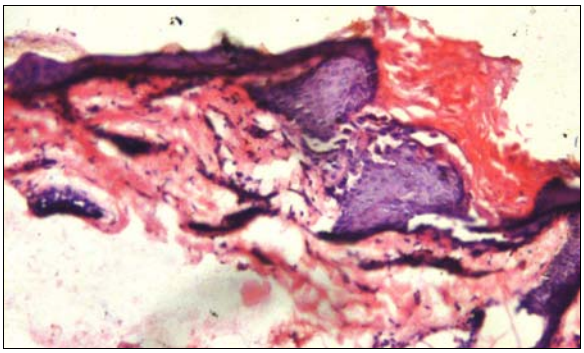

Figure-7: Low power view of skin biopsy of Darier's disease showing hyperkeratosis, suprabasal cleft with acantholytic cells, corps ronds, grains and dermal chronic inflammatory infiltrate

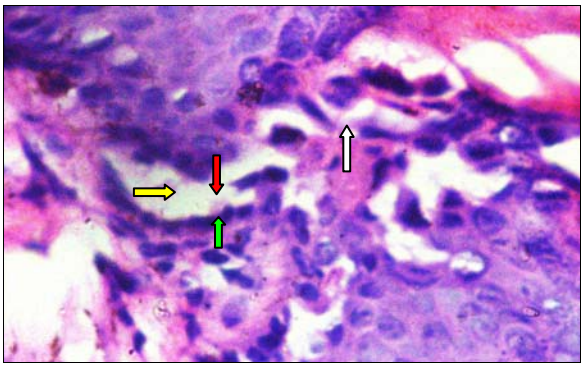

Figure-8: High power view of suprabasal cleft (⇩) with acantholytic cells (⇨), stratum basalis (⇧) & corps ronds (⇧)

DISCUSSION

Darier's disease is a rare keratinisation disorder.[1] Reported prevalence varies from 1 in 100,000 in Denmark to 30–35,000 in Northern England and Scotland.[3] The incidence of disease is reported to be 4 new cases per million, over 10 years.[9] The disease is due to mutation in the gene ATP2A2, at chromosome 12q23–24.1.[3] The gene encodes the sarcoplasmic/ endoplasmic reticulum Ca^{+2} ATPase type 2 protein (SERCA2), which is a calcium pump.SERCA2b, an isoform of SERCA2 is more widely expressed including epidermis.[3] Darier's disease is caused by reduction in SERCA2b function leading to abnormal intracellular Ca^{+2} signaling and abnormal organisation or maturation of complexes responsible for cell adhesion.[10] The mechanism of this reduction is under investigation.[11] More than 113 familial and sporadic mutations in ATP2A2 have been identified. Attempts at genotype phenotype correlations have not been successful. Family members with confirmed identical ATP2A2 mutations can exhibit differences in clinical severity of disease, suggest that other genes or environmental factors effect the expression of Darier's disease.[12]

Abnormal keratinocyte-keratinocyte adhesions and aberrant epidermal keratinisation are histological features of DD. Electron microscopy reveals loss of desmosomes, breakdown of desmosomes keratin intermediate filament attachment and perinuclear aggregates of keratin intermediate filaments.[11] There exists significant correlation between the clinical presentation of Darier's disease and intensity of histological features.[13]

Literature reports cases with isolated clinical features[1,5,9,14,15] but cases of DD with characteristic presentation are rare. Our case deserves reporting as it presents with typical features of DD and shows sporadic mutation of the concerned gene in a phenotypically normal family. About 80% of patients have mild involvement of axillae, groin, or submammary region. Facial and flexural hyper pigmentation as seen in our patient have not yet been reported. Caries teeth, gingivitis and malodouring cutaenous lesions showed presence of secondary infection. There are numerous reports of cases of DD with neuropsychiatric disorders[9] including high rates of prevalence of epilepsy, mental impairment, affective disorders but our patient was of normal intellect.

The differential diagnosis includes[3] 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 like 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.

The implications of DD are cosmetic and aesthetic.[1] Milder forms respond to general measures like improvement of hygiene, wearing cotton clothes, avoidance of heat, sunlight and use of sunscreens. Moisturizers containing urea and lactic acid, topical retinoids like adapalene, tazarotene gel, 0.1% tretinoin can decrease scaling and hyperkeratosis. Antiseptic solutions like triclosan or astringents are helpful. Topical 5-Florouracil has also been used effectively[3] Injection Boutolin toxin type A has also been used successfully for the relief of discomforting symptoms in one patient.[16]

Oral retinoids decrease hyperkeratosis, smoothen the papules and reduce odour.[3] Oral antibiotics and acyclovir are often needed to suppress secondary bacterial and viral infections. Oral contraceptives help to reduce perimenstrual flares.[4] Severe inflammatory exacerbations may respond to ciclosporin.[3] Dermabrasion[3], electrosurgery[17], laser ablations of recalcitrant plaques with CO_2,[18] ER:YAG, pulsed dye and 1,550 ηm erbium doped fractional fibre laser[19] have been successfully used. Photodynamic therapy[20] with 5 aminolevulinic acid and surgical excision of hypertrophic intertrigenous keratosis follicularis have also been reported.[21]

Patient should be informed about the complications and the care required. The emotional status should be evaluated.[9] Regardless of clinical severity and treatment options, the patient should receive genetic counselling with information on inherited condition and risk of transferring to offspring.

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