

Darier's Disease: A Rare Disorder of Keratinisation. Case Report and Review of Literature

Sujata S Giriyan¹, Archana B M²

¹Professor and Head, Department of Pathology, KIMS,Hubballi

²Post graduate student, Department of Pathology, KIMS, Hubballi

Abstract: *Background:* Darier's disease or Keratosis Follicularis, is a rare autosomal dominant disorder which is characterised clinically by appearance of multiple pruritic, discrete, scaly papules affecting seborrhoeic areas coupled with palmar pits, nail changes and mucosal involvement. Histopathology of the lesions show suprabasal clefts with acantholytic and dyskeratotic cells. Both sexes are equally affected. 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. The palmar pits are pathognomic. Darier's disease is characterized by hyperkeratotic papules that coalesce into plaques and occur primarily in seborrhoeic, but also in intertriginous areas. On rare occasion the clinical pictures is dominated by skin fragility with painful erosions and fissure. Histology shows dyskeratosis in spinous layer (Corps and Ronds) and Stratum Corneum (grains), Supra basal acantholysis and clefts (lacunae). The underlying dermal papillae, covered by a single layer of epithelium (stratum basale), project into these clefts and form villous like structures. A large keratin plug, often showing focal parakeratosis, over lies each lesion. Hyper keratosis is common.

Keywords: Autosomal dominant, palmar pits, suprabasal clefts, Darier's disease, keratosis follicularis, acantholysis, dyskeratosis

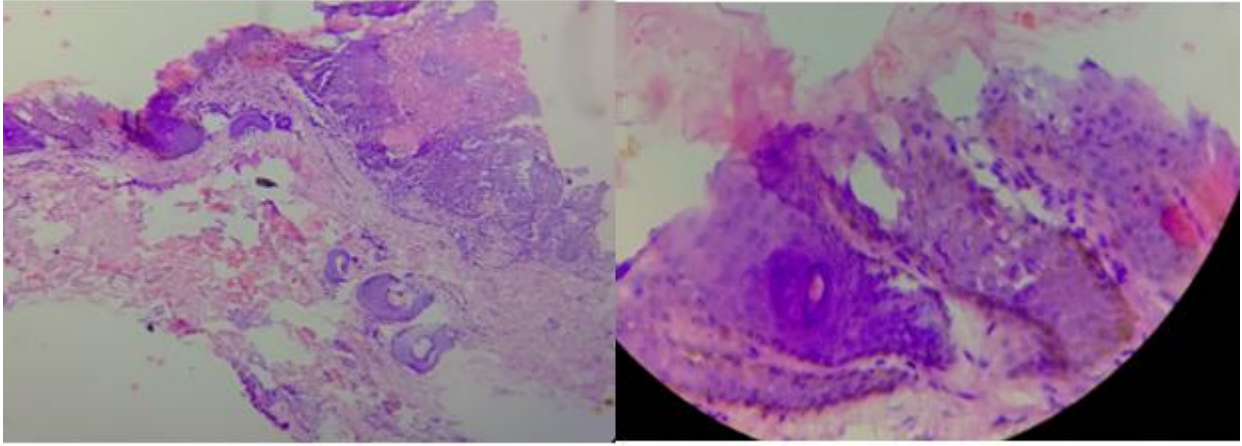
1. Case Report

Here we are presenting a case of 62 year old female who had come with complaints of skin lesions on neck, abdomen, axilla and groin on and off since eight years associated with itching. Symptoms used to be more severe during summers. On cutaneous examination, there was multiple hyper pigmented macerated papules to plaques which were ill defined on neck, bilateral inguinal region and left axilla. Nails showed longitudinal streaks. No history of oozing or discharge of pus from the lesion. Biopsy was done and sent for histopathological examination.

On histopathological examination, epidermis showed irregular acanthosis with focal area showing parabasal clefts and papillary projection with single layer of basal cells. Many dispersed epidermal cells with loss of intercellular bridges and occasional acantholytic cells were seen within the lacunae. Stratum granulosum and stratum corneum showed "corps ronds" having pale nucleus surrounded by clear hallow. Stratum corneum also showed plump, elongated nucleus with dense homogenous eosinophilic cytoplasm (GRAINS). Dermis showed scanty chronic inflammatory cell infiltrate.

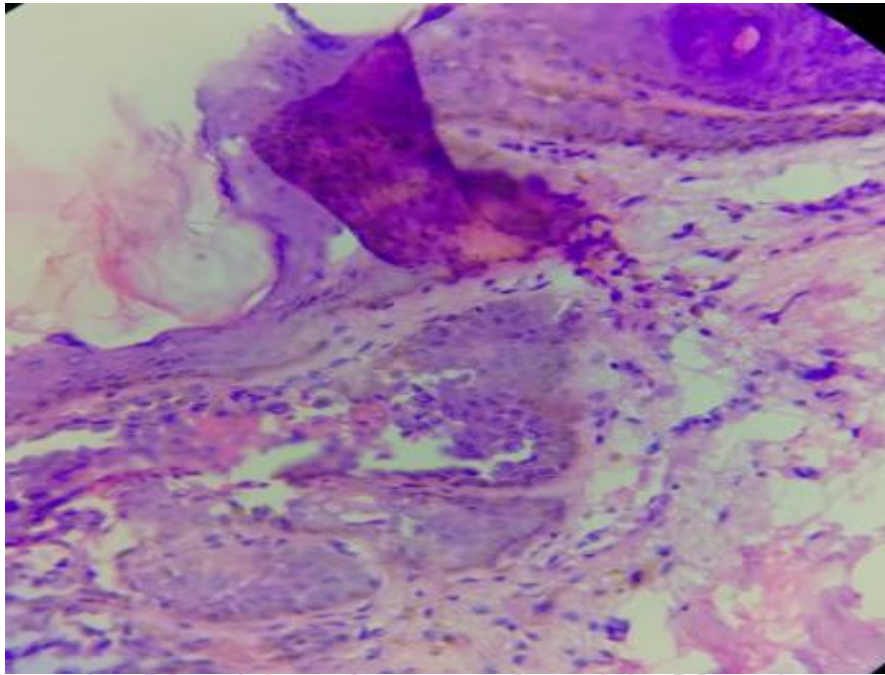
Because of the above findings, diagnosis of Darier's disease was made.



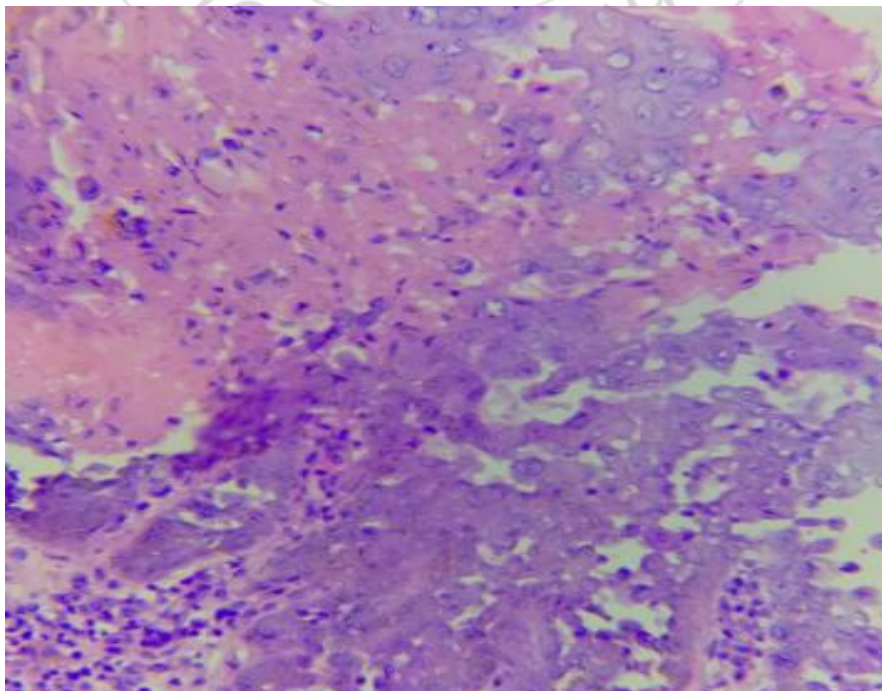


Low Power View of Darier's Disease

High Power View Showing Hyperkeratosis



High power view showing corps ronds and grains



Volume 5 Issue 10, October 2016

www.ijsr.net

Licensed Under Creative Commons Attribution CC BY

2. Discussion

Darier's disease is a rare keratinisation disorder¹. Reported prevalence varies from 1 in 1, 00,000 in Denmark⁶, 1.3 in 100,000 (Croatia)⁷, 1.8 in 100,000 (central England)⁸, 3.3 in 100,000 in western Scotland¹⁰. The incidence of disease reported to be 4 new cases per million, over 10 years⁹. The disease is due to mutation in the gene ATP2A2, at chromosome 12q23-24.1³. The gene encodes the Sarcoplasmic/Endoplasmic reticulum Ca²⁺ ATPase Type-2 Protein (SERCA2), which a Calcium pump. SERCA2b, an isoform of SERCA2 is more widely expressed including epidermis³. Darier's disease is caused by reduction in SERCA2b function leading to abnormal intracellular Ca²⁺ signalling and abnormal organisation or maturation of complexes responsible for cell adhesion¹¹.

Histologically studies of Darier's disease have suggested that there was an abnormality in the complex formed by desmosomes with keratin filaments that leads to a defect in the cell-cell adhesion. Desmosomes are the prime adhesion junctions in the epidermis¹⁵⁻¹⁷. Ca²⁺ is known to have a role in the development of epithelial junctions and in regulating cell differentiation^{18,19}. The assembly of desmosomes in epithelial cells in-vitro is initiated through an increase in the extracellular Ca²⁺ concentration^{20,21}, but variations in intracellular Ca²⁺ are also thought to be important in regulating epithelial cell to cell adhesion¹⁵. The intracellular Ca²⁺ concentration is determined by relative activities of the Ca²⁺ pumps and Ca²⁺ channels²¹. Changes in intracellular Ca²⁺ concentration occur especially at the sites of junction and assembly of epithelial cells²². SERCA2 influences adhesion between keratinocytes as well as cellular differentiation in the epidermis, especially the isoform SERCA2b which is abundantly expressed in epidermis and its appendages⁵.

Patients with Darier's disease who are heterozygous for mutated ATP2A2 allele will have only partial deficiency of the SERCA2 pump⁵. Sakuntabhai et al postulated that Darier's disease patients will exhibit altered Ca²⁺ signalling in epidermal cells, possibly through the alteration of cytosolic Ca²⁺ oscillations⁵. This may trigger a cascade of events involving the phosphorylation of target proteins, the regulation of gene transcription²³⁻²⁶ or the transport of desmosomal proteins to the plasma membrane, resulting in impaired desmosome assembly or altered anchorage of cytokeratin filaments to the desmosomal plaque⁵.

Microscopically, Darier's disease shows non-specific features which include hyperkeratosis, papillomatosis, increased granular layer, and acanthosis with follicular keratotic plugs. Specific features include dyskeratotic cells which are corps ronds that is round cells with eosinophilic condensed cytoplasm and pyknotic nucleus found in stratum malpighii. Grains that is dense eosinophilic spindle shaped cells with a small nucleus, found in stratum corneum.

They look like large parakeratotic cells. Other features include clefts within stratum malpighii into which villous growth of epidermis lined by single layer of basal cells may project into. Dermis shows mild lymphoid infiltrate. There exists significant correlation between the clinical

presentation of Darier's disease and intensity of histological features¹⁴.

Histologically the disease needs differentiation from benign familial pemphigus, Grover's disease and pemphigus vulgaris. Immunofluorescence of skin biopsy differentiate different acantholytic disorders³.

Electron microscopy reveals loss of desmosomes, breakdown of desmosome keratin intermediate filament attachment and perinuclear aggregates of keratin intermediate filaments¹². The differential diagnosis includes Acne Vulgaris, seborrheic dermatitis, Acanthosis nigricans, Confluent reticulate papillomatosis, Prurigo pigmentosa and reticulate erythematous mucinosis syndrome. In Acanthosis nigricans, lesions are more pigmented. Confluent reticulate papillomatosis, lesions are flat and confined to the upper trunk. The harshness of papules on palpation helps to distinguish it from visually similar conditions like Prurigo pigmentosa and reticulate erythematous mucinosis syndrome⁵.

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 affect the expression of Darier's disease¹³.

3. Conclusions

Darier's disease is a rare autosomal dominant disorder with ATP2A2 mutation. Mutations affect activity of the endoplasmic ATPase isoform 2. Whether there is an exact correlation between activity of the ATPase and phenotype of the disease remains unclear and demands further investigations.

References

- [1] Cardoso CL, Freitas P, Taveira LAA, Consolaro. Med Oral Patol Oral Cir Bucal 2006;11(5):E404-6.
- [2] Munro CS The phenotype of Darier's disease: penetrance and expressivity in adults and children. Br J Dermatol 1992;127:126-30
- [3] Judge MR, McLean WHI, Munro CS. Disorders of keratinization. In: Burns T, Breathnach S, Cox N, Griffiths, eds. Rook's Textbook of Dermatology 8th edition, Vol. 1. Massachusetts, Oxford, Victoria: Blackwell science: 2010. P.19.81-6.
- [4] Kwok PY, Bhutani T, Liao W. Keratosis follicularis (Darier Disease). 2010. Available at: <http://emedicine.Medscape.com/article/1107340-overview#a0101>.
- [5] Sakuntabhai A, Ruiz-Perez V, Carter S et al. Mutations in ATP2A2, encoding a Ca²⁺ pump, cause Darier disease. Nat Genet 1999;21:271-7.
- [6] Svendsen IB, Albrechtsen B. The prevalence of dyskeratosis follicularis (Darier's disease) in Denmark. Acta Dermato-Venereol 1959;39:256-69.
- [7] Sokol J, Kinsky A. Follicular dyskeratosis (Mb Darier) in Croatia. Acta derm iug 1991;18:57-66.

- [8] Wilkinson JD, Marsen RA, Dawber RPR. Review of Darier's disease in the Oxford region. *Br J Dermatol* 1977;15:13.
- [9] Cordeiro Q Jr, Werebe DM, Vallada H. Darier's disease : a new paradigm for genetic studies in psychiatric disorders. *Sao Paulo Med J* 2000;118;201-3
- [10] Tavadia S, Mortimer E, Munro CS. Genetic epidemiology of Darier's disease: a population study in the west of Scotland. *Br J Dermatol* 2002; 146:107-9.
- [11] Dhitavat J, Fairelough RJ, Hovanian A, Burge SM. Calcium pumps and keratinocytes: lessons from Darier's disease and Hailey-Hailey disease. *Br J Dermatol* 2004;150:821-8.
- [12] Muller EJ, Caldelari R, Kolly C, Williamson I, Baumann D, Richard G, et al. consequences of depleted SERCA2-gated calcium stores in the skin. *J Invest Dermatol* 2006;126:721-31.
- [13] Bechetnia M, Charfeddine C, Kassar S, Ziribi H, Guettiti Ht, Ellouze F, et al. Clinical and mutational heterogeneity of Darier's disease in Tunisian families. *Arch Dermatol* 2009;145:654-6.
- [14] Kassar S, Tounsi-Kettiti, Charfeddine C, Zribi H, Bchetnia M, Jerbi E, et al. histological characterization of Darier's disease in Tunisian families. *J Eur Acad Dermatol Venerol* 2009;23:1178-83.
- [15] Burdett IDJ. Aspects of the structure and assembly of desmosomes. *Micron* 1998 ; 29: 309-28.
- [16] Burge S. cohesion in the epidermis. *Br J Dermatol* 1994;131 : 153-9.
- [17] Garrod DR, Chidgey MAJ, North AJ. Desmosomes: differentiation, development, dynamics and disease. *Curr Opin cell Biol* 1996; 8; 670-8.
- [18] Berridge MJ, Bootman MD, Lipp P. Calcium-a life and death signal. *Nature* 1998; 395: 645-8.
- [19] Stuart RO, Sun A, Bush KT, et al. Dependence of epithelial intercellular junction biogenesis on the thapsigargin-sensitive intracellular calcium stores. *J Biol Chem* 1996;271: 13636-41.
- [20] Duden R, Franke WW. Organization of desmosomal plaque proteins in cells growing at low calcium concentrations. *J Cell Biol* 1988; 107: 1049-63.
- [21] Watt FM, Matthey DL, Garrod DR. Calcium-induced reorganization of desmosomal components in cultured human keratinocytes. *J Cell Biol* 1984; 99: 2211-5.
- [22] Nigam SK, Rodriguez-Boulan E, Silver RB. Changes in intracellular calcium during the development of epithelial polarity and junctions. *Proc Natl Acad Sci USA* 1992; 209: 6162-6.