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

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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 anddyskeratotic cells.scence[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 pathognomic[3].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[1, 2, 3].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 (stratumbasale), 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.[3, 4]***

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

1. Case Report

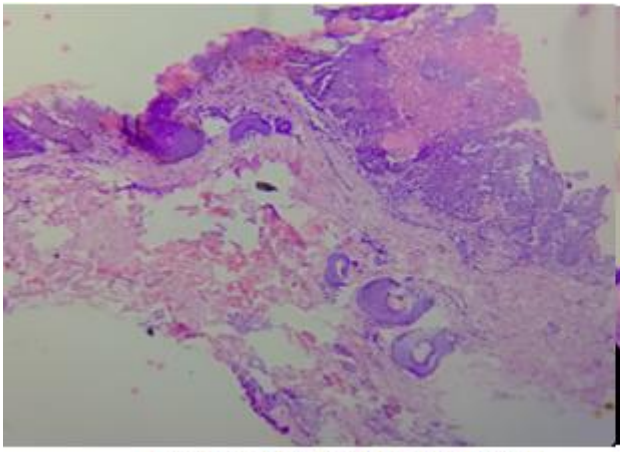
Here we are presenting a case of 62 year old female who had come with complaints of skin lesions on neck, abdomen, axilla and groin on and off since eight years associated with itching. Symptoms used to be more severe during summers. On cutaneous examination, there was multiple hyper pigmented macerated 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 andoccasional acantholytic cells were seen within the lacunae. Stratum granulosumand 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.

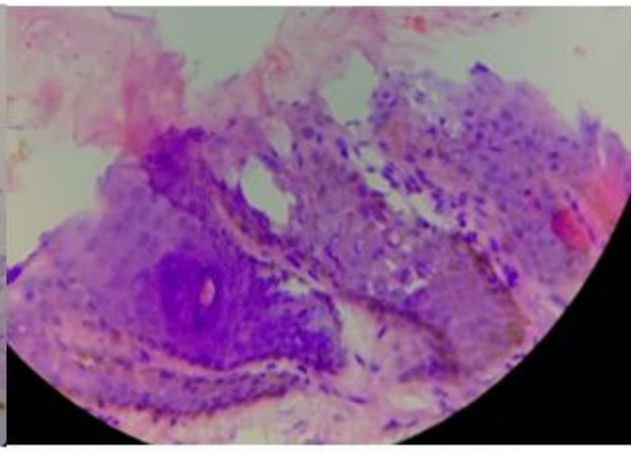
Because of the above findings, diagnosis of Darier's disease was made.



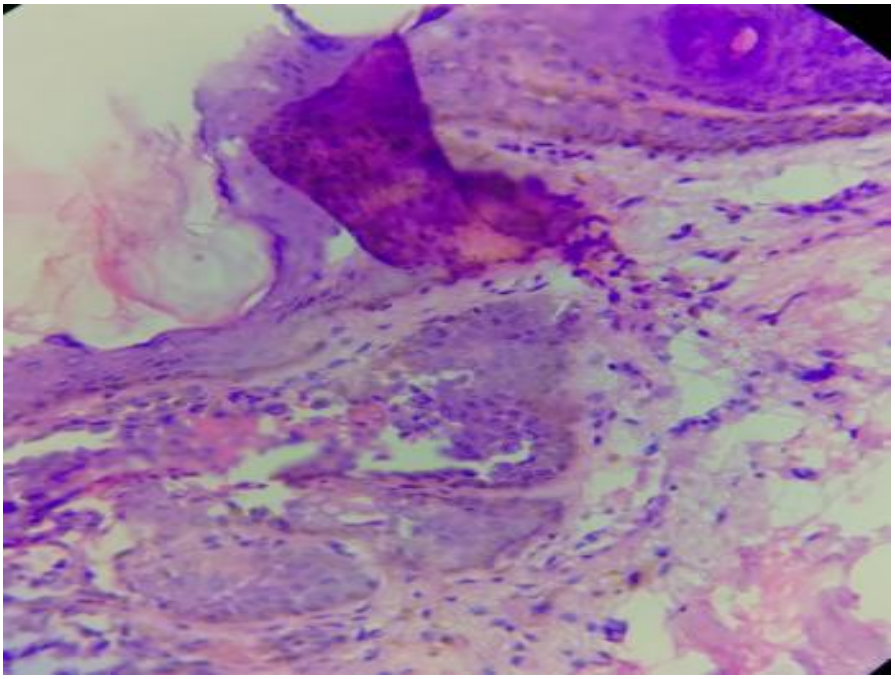
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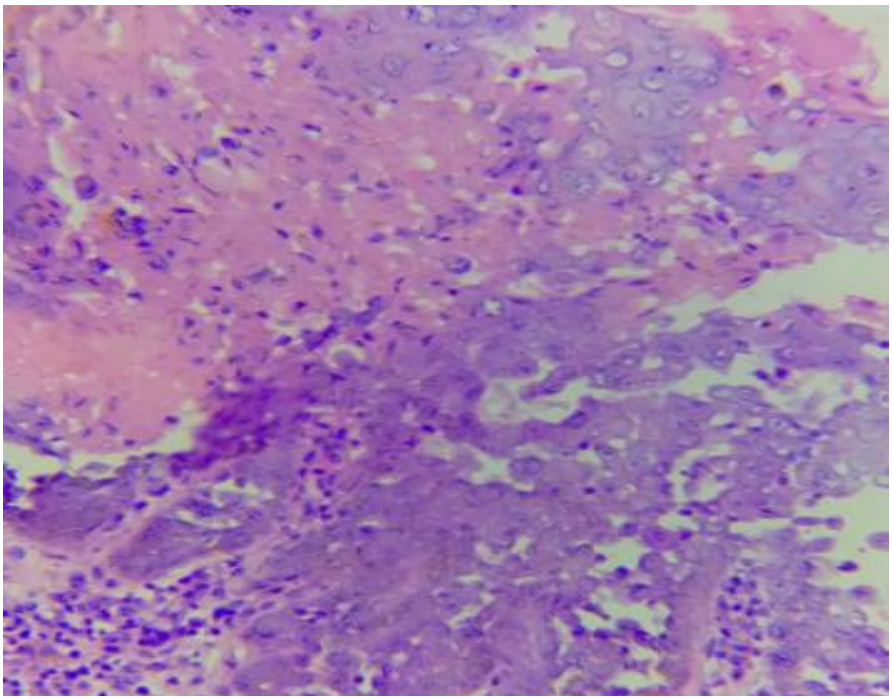
Low Power View of Darier's Disease



High Power View Showing Hyperkeratosis



High power view showing corps ronds and grains



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2. Discussion

Darier's disease is a rare keratinisation disorder[1]. Reported prevalence varies from 1 in 1, 00,000 in Denmark[6], 1.3 in 100,000 (Croatia) [7],1.8 in 100,000(central England)[8].3.3 in 100,000 in western Scotland[10] . The incidence of disease 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 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 signalling and abnormal organisation or maturation of complexes responsible for cell adhesion[11].

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 epidermis[15-17]. Ca^{2+} 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 Ca^{2+} concentration[20,21], but variations in intracellular Ca^{2+} are also thought to be important in regulating epithelial cell to cell adhesion[15]. The intracellular Ca2+ concentration is determined by relative activities of the Ca2+ pumps and Ca2+ channels[21]. Changes in intracellular Ca2+ concentration occur especially at the sites of junction and assembly of epithelial cells[22]. 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 appendages[5].

Patients with Darier's disease who are heterozygous for mutated ATP2A2 allele will have only partial deficiency of the SERCA2 pump[5]. Sakuntabhaietal postulated that Darier's disease patients will exhibit altered Ca^{2+} signalling in epidermal cells, possibly through the alteration of cytosolic Ca^{2+} oscillations[5]. This may trigger a cascade of events involving the phosphorylation of target proteins, the regulation of gene transcription[23-26] or the transport of desmosomal proteins to the plasma membrane, resulting in impaired desmosome assembly or altered anchorage of cytokeratin filaments to the desmosomal plaque[5].

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 pyknoticnucleus found in stratum malphigii. Grains that is dense eosinophilic spindle shaped cells with a small nucleus, found in stratum corneum.

They look like large parakeratoticcells. Other features include clefts within stratum malphigii 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 ofhistological features[14].

Histologically the disease needs differentiation from benign familial pemphigus, Grover's disease and pemphigus vulgaris. Immunofluorescence of skin biopsy differentiate different acantholytic disorders[3].

Electron microscopy reveals loss of desmosomes, breakdown of desmosome keratin intermediate filament attachment and perinulcear aggregates of keratin intermediate filaments[12]. The differential diagnosis includes Acne Vulgaris, seborrheic dermatitis, Acanthosisnigricans, Confluent reticulate papillomatosis, Prurigopigmentosa and reticulate erythematomucinous syndrome. In Acanthosisnigricans, 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 Prurigopigmentosa and reticulate erythematomucinous syndrome[3].

More than 113 familial and sporadic mutations in ATP2A2 have been identified.Attempts at genotypephenotype 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 affectthe expression of Darier's disease[13].

3. Conclusions

Dariers disease is a rare autosomal dominant disorder with ATP2A2 mutation. Mutations affect activity of the endoplasmic ATPase isoform2. Whether there is an exact correlation between activity of the ATPase and phenotype of the disease remains unclear and demands further investigations.

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