Molecular Pathogenesis and Complications Associated with Keratosis Follicularis

Hira Ghani B.A.[1], Marielle Jamgochian M.B.S.[2], Stefanie Cubelli D.O.[3]

1 NYIT College of Osteopathic Medicine, Old Westbury, NY
2 Department of Dermatology, Robert Wood Johnson, Somerset, NJ
3 Department of Dermatology, St. John's Episcopal Hospital, Far Rockaway, NY

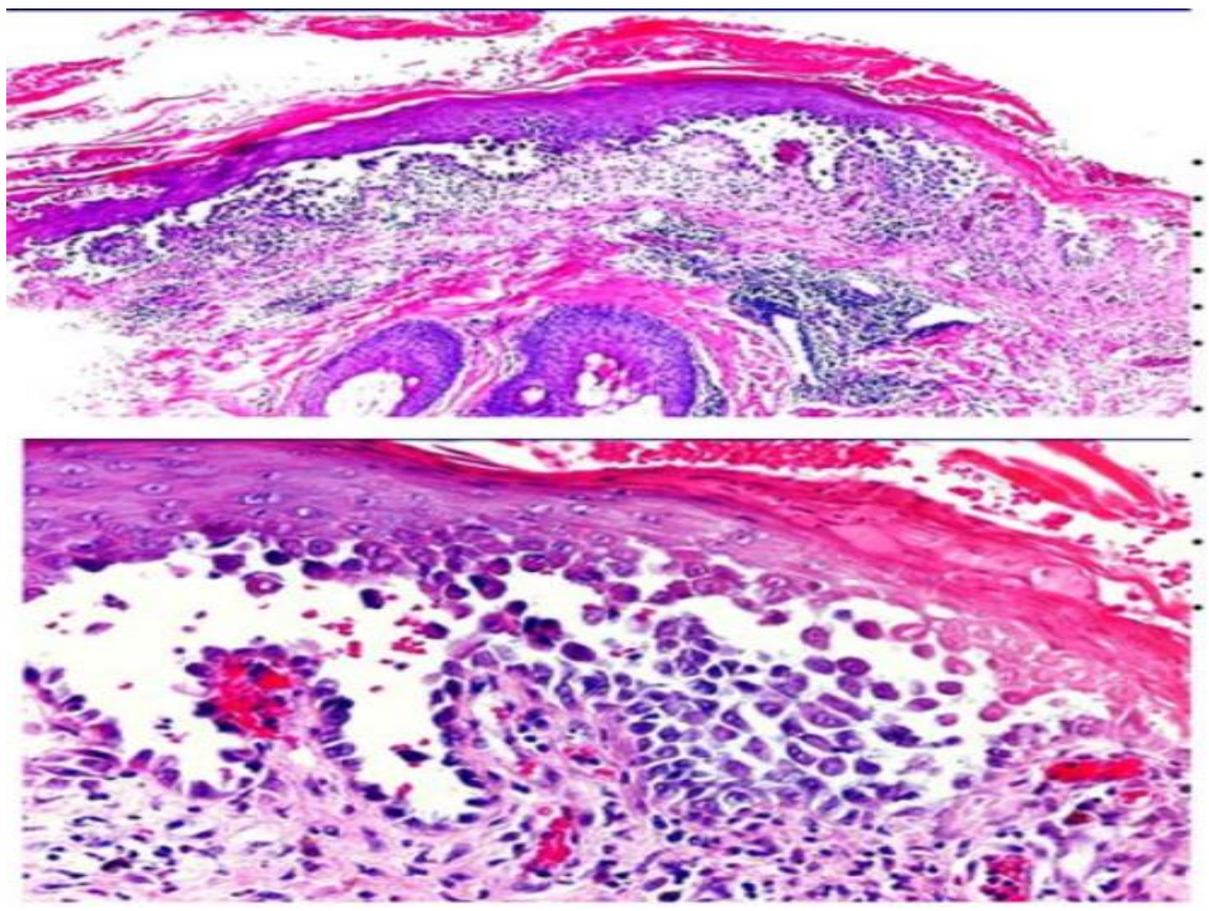
Introduction

Keratosis follicularis (KF), or Darier's disease (DD), is a rare autosomal dominant disorder characterized by the appearance of multiple scaly hyperkeratotic papules affecting seborrheic areas. These papules may become hypertrophic, malodorous, painful and prone to secondary infections. KF affects approximately 1 in 36,000 individuals, and typically presents in the first or second decade of life. DD is caused by genetic defects in ATP2A2 encoding sarcoplasmic/endoplasmic reticulum Ca(2+)-ATPase isoform 2 (SERCA2), which eventually results in loss of cell-to-cell adhesion and abnormal keratinization. DD is associated with various basal cell carcinomas (BCC) and other skin cancers, nail changes, ocular/mucosal manifestations and neuropsychiatric disorders. Additionally, individuals with DD have a greater risk of being diagnosed with Type 1 Diabetes Mellitus as well as disease-specific heart failure.

Discussion

- DD may have nail involvement (subungual hyperkeratosis and red/white longitudinal bands with pathognomonic notch at the nail free margin), oral mucosal involvement (white papules on the buccal mucosa, palate, and gingiva), and rarely, ocular manifestations (corneal ulcerations, conjunctival keratosis and recurrent herpes keratitis)
- ATP2A2 loss of function mutation leading to disruption of Ca2+homeostasis and reduced expression of the antiapoptotic proteins Bcl-2 and Bcl-XL may contribute to increased BCC prevalence in individuals with DD
- Increased prevalence of bipolar disorder (4.3 fold increase) and schizophrenia (2.3 fold increase) due to genetic variability in ATP2A2 gene are also noted
- Associated with Type I Diabetes Mellitus, as SERCA2b loss secondary to ATP2A2 mutations leads to secretory dysfunction and decreased beta cell survival
- Heart disease may be associated with DD, as pre-existing cardiac conditions can be exacerbated by the ATP2A2 mutations.
- Treatment with oral and topical retinoids is generally recommended for mild to moderate DD
- Dermabrasion and carbon dioxide/YAG laser are reserved for severe and refractory cases
- UV light exposure exacerbates the condition; therefore, individuals with DD should avoid direct sunlight and use broad spectrum UV protection daily

Results



Hematoxin and Eosin Magnification of DD

- Irregular acanthosis, papillomatosis, hyperkeratosis
- Corps (basophilic cells with dark pyknotic nuclei and perinuclear halo) in the granular layer
- Dermal chronic inflammation

Conclusion

Darier's disease is a rare, autosomal dominant disorder with multisystem involvement. Mucosal, nail and ocular changes are sometimes observed, and those with DD may be more likely to be diagnosed with psychiatric conditions, type I D iabetes, and heart disease. DD may also be associated with BCC and other skin cancers. It is crucial for dermatologists to anticipate and discern extracutaneous manifestations associated with DD to provide holistic, interdisciplinary care along with timely and appropriate referral to other specialists for further management.

References

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Contact
Hira Ghani, BA
Medical Student
NYITCOM
hghani01@nyit.edu

Disclosures: None