https://doi.org/10.48047/AFJBS.6.15.2024.4672-4684

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Darier's Disease: A Case Series Compendium.

Dr. Prarthana. R*, Dr. Sivayogana. R, Dr. Kumaravel Sadagopan, Dr. Rajesh. R, Dr. Ravikanth. P, Dr. Nirmala. R.

Postgraduate, Department of Dermatology, Venereology and Leprosy, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Kanchipuram.
Assistant Professor, Department of Dermatology, Venereology and Leprosy, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Kanchipuram.
Professor and Head of the Department, Department of Dermatology, Venereology and Leprosy, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research,Kanchipuram.
Professor, Department of Dermatology, Venereology and Leprosy, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research,Kanchipuram.
Senior Resident, Department of Dermatology, Venereology and Leprosy, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research,Kanchipuram.
Senior Resident, Department of Dermatology, Venereology and Leprosy, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research,Kanchipuram.

Corresponding Author:Dr. Prarthana. R,
Postgraduate, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Kanchipuram, Tamil Nadu, India- 631552.
Number- +91 9445675353
Email id: prarthanaraja777@gmail.com

Volume 6, Issue 15, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 05 Sep 2024

doi: 10.48047/AFJBS.6.15.2024.4672-4684

ABSTRACT:

INTRODUCTION:

Darier's disease is a rare genetic skin disorder characterized by multiple hyperkeratotic, greasy papules primarily affecting seborrheic areas, associated with nail abnormalities and mucous membrane involvement. It follows an autosomal dominant inheritance pattern due to mutations in the ATP2A2 gene, impacting calcium signalling and cellular adhesion.

CASE SERIES:

This study presents four cases of Darier's disease, showcasing the diverse clinical spectrum of the disease. Cases 1, 2, and 3 depict the typical presentation of the disease with chronic, relapsing keratotic papules exacerbated by sun exposure and other factors, while emphasising the familial inheritance patterns. Case 4 highlights a rare Type 1 segmental variant with unilateral distribution along the lines of Blaschko.

CONCLUSION:

Diagnosis of Darier's disease relies on clinical evaluation and histopathological examination which crucial for differentiating Darier's disease from other dermatoses and to provide insight to the patients about its hereditary implications. Treatment options, including topical and systemic therapies alongside lifestyle modifications, aim to manage symptoms and improve patient quality of life despite the lack of a definitive cure.

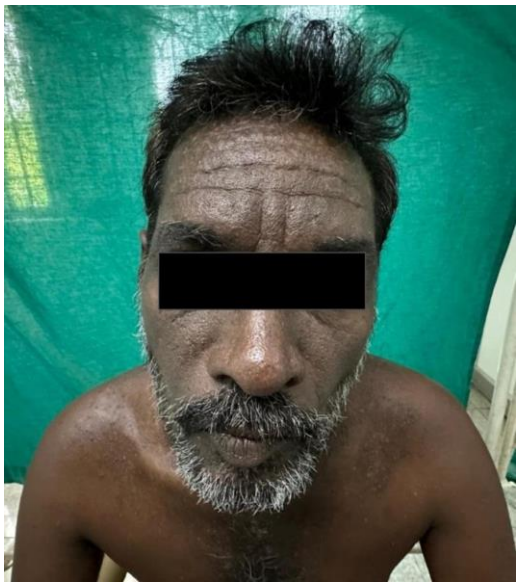
KEYWORDS: Darier's disease, Blaschko lines, SERCA2.

INTRODUCTION:

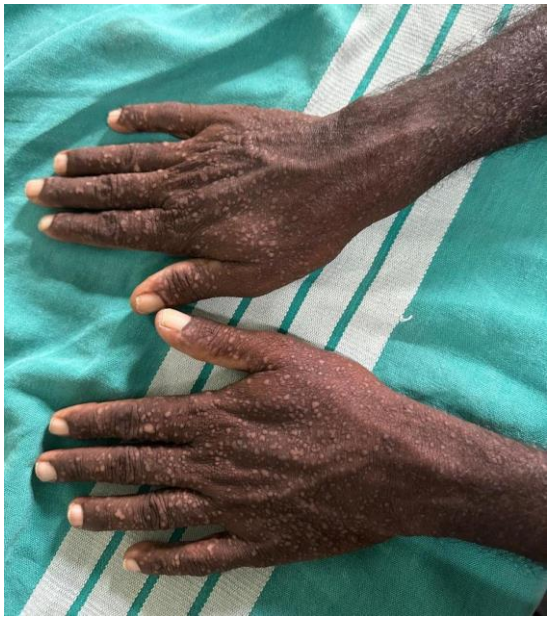
Darier's disease is a rare, slowly progressing genetic skin disorder that follows an autosomal dominant inheritance pattern. It is characterized by persistent eruption of hyperkeratotic, greasy papules, predominantly over the seborrheic areas of the body. This condition is often associated with nail abnormalities and occasionally affects the mucous membranes. The disease is caused by mutations in the ATP2A2 gene located on chromosome 12q23-24.1, which encodes the SERCA2 intracellular calcium pump responsible for maintaining low cytoplasmic calcium levels. SERCA2 is crucial for calcium signal transduction, and its impairment leads to the disruption of intercellular junctions and cellular adhesion. Clinically, Darier's disease presents with multiple keratotic papules, and histological examination reveals a loss of adhesion between epidermal cells and dyskeratosis.

CASE 1:

A 40-year-old man presented with a chronic, relapsing, and remitting history of multiple itchy, blackish, raised lesions on his face, upper chest, and upper back, along with history of several raised, skin-colored lesions on both forearms .These lesions predominantly appeared over the sun-exposed areas, and the patient reported worsening of symptoms with prolonged sun exposure. He reported a similar history of complaints in his father. On examination, multiple hyperpigmented, hyperkeratotic greasy papules and plaques were observed on his face, upper-chest and upper-back (Figure1). Additionally, multiple flat-topped, symmetrical, skin-colored to hypopigmented keratotic papules were present on the dorsum of both hands, resembling that of acrokeratosis verruciformis lesions (Figure 2). Biopsy was taken from his upper-back and dorsum of right hand and histopathological examination led to a conclusive diagnosis of Darier's Disease evidenced by parakeratosis, acanthosis, acantholysis and dyskeratosis forming corps and rods. Patient was started on oral acitretin and topical keratolytics . Patient was advised on strict sun protection and lifestyle modifications. Improvement of the skin lesions was noted and the patient is currently on regular follow up.



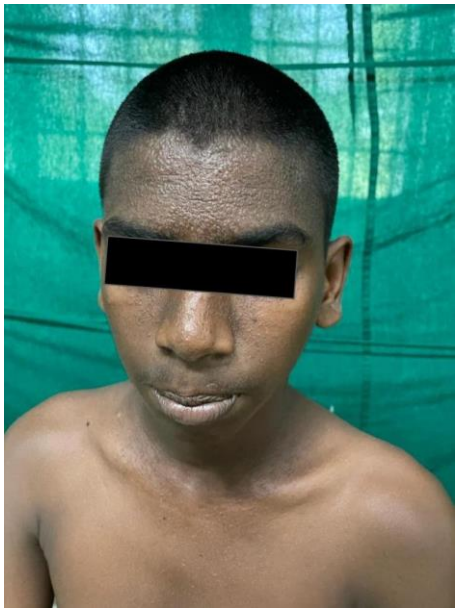
[Figure 1] : Multiple Hyperpigmented, Hyperkeratotic papules coalescing to form plaques over face.



[Figure 2] : Multiple flat-topped, symmetrical, skin-coloured to hypopigmented keratotic papules present on the dorsum of bilateral hands.

CASE 2:

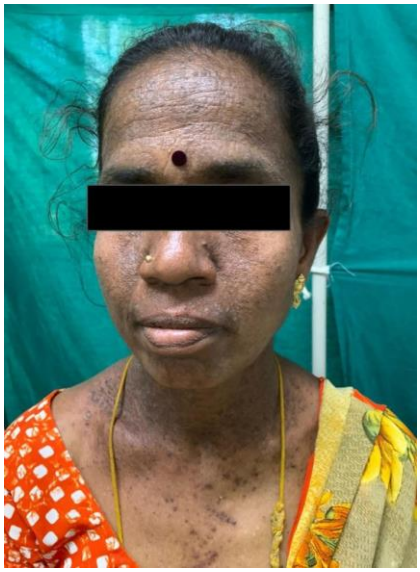
A 17-year-old male presented with numerous skin coloured to dark, raised skin lesions over seborrheic areas - scalp, face, and neck for the past 10 years associated with itching and burning sensation, especially upon sun exposure .History of similar complaints were present in his father. On examination, multiple hyperpigmented, hyperkeratotic, greasy, flat-topped papules were observed, with some coalescing into plaques on his scalp, face, and neck (Figure 3).Hyperpigmentation of oral mucosa was observed. A biopsy was taken, and histopathological examination revealed features suggestive of Darier's Disease. Patient was started on oral acitretin, topical adapalene , moisturiser and advised strict sun protection. Patient is on regular follow-up and showing improvement in symptoms.



[Figure 3] : Multiple hyperpigmented, hyperkeratotic greasy papules and plaques over face and neck.

CASE 3:

A 43 year old Female presented with a 15 year long history of pruritic, mildly scaly, dark colored, raised skin lesions involving the seborrheic regions such as the face, neck, chest and upper-back .History of exacerbation of symptoms on exposure to Sunlight, heat and sweating was present. On examination, multiple hyperpigmented, hyperkeratotic, greasy papules and plaques were present over the face, neck, chest and upper back giving a characteristic dirty warty appearance (Figure 4 and 5).Mild scaling was also noted over face and neck. Biopsy was done and Histopathological study revealed features confirmative of Darier's Disease. Patient was started on oral acitretin, emollients and sunscreen. Patient is on regular follow-up.



[Figure 4]

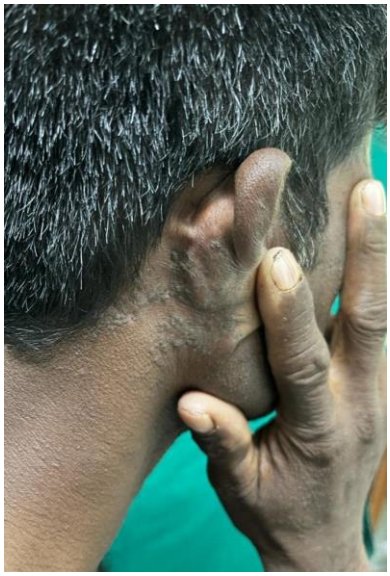
[Figure 5]

[Figure 4 and 5] : Multiple hyperpigmented, hyperkeratotic, greasy papules , few coalescing to form plaques with mild scaling seen over face , neck and chest.

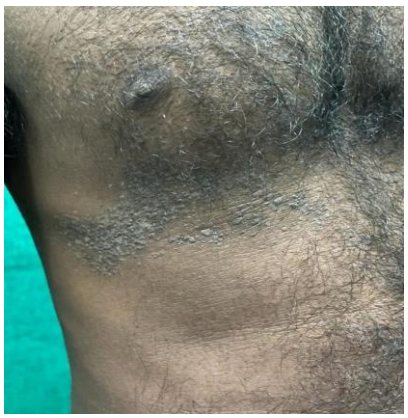
CASE 4:

A 42-year-old male presented with a history of intensely pruritic, blackish, raised lesions on the right side of his face, shoulder, trunk, and right leg for the past 20 years with periods of exacerbation and remission since adolescence. On examination, multiple hyperpigmented, hyperkeratotic papules and plaques were observed on the right side of his face, post-auricular

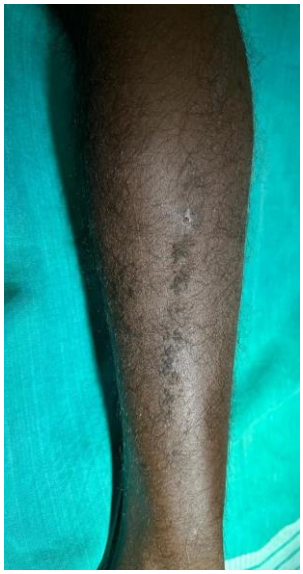
region, shoulder, trunk, and posterior aspect of his right lower limb, distributed along the lines of Blaschko (Figure 6,7 and 8). A skin biopsy was performed, and histopathological examination showed parakeratosis, acanthosis, acantholysis, and dyskeratosis with the presence of corps ronds and grains. Based on the clinical presentation and histopathological findings, a diagnosis of Type 1 segmental Darier's disease was made. Patient was started on oral retinoids and topical keratolytic agents. Patient is on regular follow up.



[Figure 6]



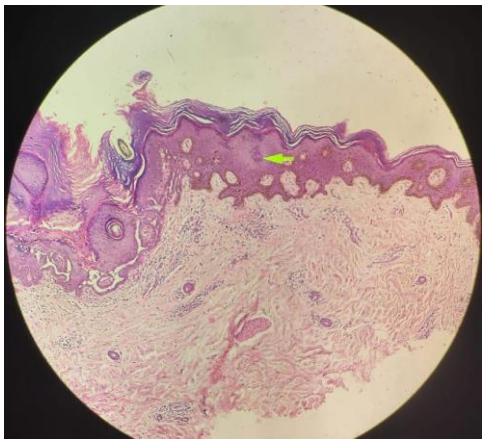
[Figure 7]



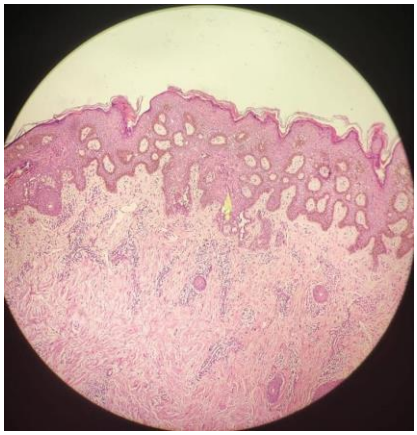
[Figure 8]

[Figure 6,7 and 8]: Hyperpigmented, Hyperkeratotic papules and plaques in blaschkoid distribution over Right side of face- post auricular region, Right side of trunk and posterior aspect of Right lower limb respectively.

SKIN BIOPSY: HISTOPATHOLOGICAL EXAMINATION



[Figure 9]



(Figure 10)

[Figure 9 and 10] : HPE - H and E ,10X , Showing parakeratosis, acanthosis, acantholysis with dyskeratosis forming corps and rods and features suggestive of Darier's Disease.

DISCUSSION:

Darier's Disease, also known as Darier-White disease or follicular keratosis, is a rare autosomal dominant genodermatosis first described by Darier and White in 1889. The prevalence is estimated to be between 1:30,000 and 1:100,000, affecting both males and females equally. The disease typically manifests during the first two decades of life, often peaking during puberty. Darier's Disease is caused by a mutation in the ATP2A2 gene, which encodes SERCA2 , a calcium pump in the endoplasmic reticulum membrane. This mutation impairs intercellular adhesion, leading to the hallmark clinical manifestations.[1]

Clinically, Darier's Disease is characterized by multiple keratotic, greasy papules that can coalesce into plaques, predominantly affecting seborrheic areas such as the trunk, scalp, forehead, and flexures giving a characteristic dirty warty appearance. These lesions are generally symmetrical and can be exacerbated by heat, sun exposure, sweating, friction, and stress. The disease can also involve nail abnormalities, mucosal involvement, and occasionally neuropsychiatric symptoms. Additionally, around 10% of patients present with localized lesions in patterns like unilateral, linear, segmental, and zosteriform distributions. [2]

Segmental Darier's Disease is an uncommon variant of the disease, which results from genetic mosaicism with only a few cases reported in the literature. It is classified into two types: Type 1 Segmental Darier's Disease results from a postzygotic, somatic mutation in the ATP2A2 gene, causing unilateral, localized eruptions along the lines of Blaschko. Type 2 Segmental Darier's Disease involves a germline mutation in the ATP2A2 gene, along with a postzygotic mutation in the other allele. This leads to localized areas of increased severity within a background of milder, generalized Darier's Disease. Patients with Segmental Darier's Disease typically present later in life, around the fourth or fifth decade. The condition appears as unilateral eruptions of erythematous and keratotic vesicles and papules following the lines of Blaschko. Symptoms often worsen with heat and sweating, and hyperpigmentation of the oral mucosa may be observed. [3-7]

Diagnosis of Darier's Disease is usually confirmed through skin biopsy and histopathological examination. Key histological features include suprabasal acantholysis with corps ronds and grains: Corps ronds are acantholytic enlarged keratinocytes in the Malpighian layer with darkly staining, partially fragmented nuclei, clear cytoplasm, and a bright ring of collapsed keratin bundles. Grains are small, oval cells in the stratum corneum with intensely eosinophilic cytoplasm composed of collapsed keratin bundles containing shrunken parakeratotic nuclear remnants. [7]

Differential diagnoses for generalized Darier's Disease include Hailey-Hailey disease, Grover disease, lichen planus, psoriasis, and pityriasis rubra pilaris. For segmental Darier's Disease, differentials include herpes zoster, linear nevoid disorders, lichen striatus, and lichen planus. Notably, acrokeratosis verruciformis of Hopf, a rare genodermatosis, is often considered a variant of Darier's Disease due to shared ATP2A2 mutations. Skin biopsy and histopathological study is crucial for diagnosing Darier's disease and distinguishing it from the other differential diagnosis. Since Darier's is an autosomal dominant disorder, accurate diagnosis helps in counseling the patients about its hereditary nature and potential impact on their offsprings. [8]

Treating Darier's Disease remains challenging due to the lack of validated curative options. Several treatments are reported in the literature with limited effectiveness. First-line treatments include topical corticosteroids or retinoids.For persistent symptoms, topical retinoids like tretinoin, adapalene, or tazarotene are recommended. Systemic retinoids may be

considered for severe and extensive cases. Sunscreen and emollients are essential for symptom management. Lifestyle modification measures such as avoiding triggers, improving hygiene, wearing cotton clothes, and using emollients and sunblock are generally sufficient for controlling symptoms in less severe cases. Topical keratolytic agents such as salicylic acid and lactic acid can improve lesions by reducing hyperkeratosis. Topical antibiotics like fusidic acid and mupirocin help reduce secondary bacterial colonization and malodour. Other alternatives include 5-fluorouracil, calcineurin inhibitors, and synthetic vitamin D3 analogue. [9-10]

For generalized Darier's Disease, systemic retinoids like isotretinoin and acitretin are the most effective treatments. Other systemic therapies include cyclosporine, oral contraceptives, and doxycycline, which helps correct cellular calcium imbalance by chelating and assisting calcium in crossing membranes. In chronic recalcitrant cases , other treatment modalities include dermabrasion, electrosurgery, ablative lasers, photodynamic therapy, and surgical excision can also be considered. [9-11]

CONCLUSION:

Darier's Disease is a rare, genetically inherited dermatological disorder characterized by significant clinical variability and therapeutic challenges. The cases presented in this study highlight the diverse manifestations of Darier's Disease, ranging from common presentations to the rare segmental variant.

Cases 1, 2, and 3 exemplify typical presentations of Darier's Disease, characterized by multiple hyperkeratotic, greasy papules in seborrheic areas, with symptoms exacerbated by sun exposure, heat, sweating etc. These cases also highlight the chronic and relapsing nature of the disease. Notably, Cases 2 and 3 highlight the influence of autosomal dominant inheritance, with a family history evident in the parents of both cases , underscoring the genetic significance in disease transmission. Case 4 introduces the rare Type 1 segmental variant, marked by unilateral distribution along the lines of Blaschko, a presentation that constitutes only 10% of Darier's Disease cases and is infrequently reported in the literature. The segmental variant, although rare, should be included in the differential diagnosis of linear dermatoses.

Accurate diagnosis through clinical evaluation and histopathological study are crucial for diagnosing Darier's disease and distinguishing it from other dermatoses so as to provide counselling to the patients about its autosomal dominant inheritance and potential risk to the offsprings. Despite the lack of a definitive cure, a combination of topical and systemic therapies, along with lifestyle modifications, can significantly improve patient outcomes. The diverse presentations among these cases highlight the importance of tailored treatment approaches to manage symptom severity and lesion distribution effectively.

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