

# Darier's Disease: A Clinical Rarity

<sup>1</sup>Roopa S Rao, <sup>2</sup>Vijaya V Mysorekar, <sup>3</sup>Sumathy TK

<sup>1</sup>Professor, Department of Oral Pathology, MS Ramaiah Dental College, Bengaluru, Karnataka, India

<sup>2</sup>Professor, Department of Pathology, MS Ramaiah Medical College and Hospital, Bengaluru, Karnataka, India

<sup>3</sup>Professor and Head, Department of Dermatology, MS Ramaiah Medical College and Hospital, Bengaluru, Karnataka, India

**Correspondence:** Roopa S Rao, Professor, Department of Oral Pathology, MS Ramaiah Dental College, Bengaluru, Karnataka India, e-mail: drroopasrao1971@gmail.com

## ABSTRACT

Darier's disease (DD) is a rare autosomal dominant genodermatosis clinically manifested by greasy hyperkeratotic papules primarily affecting seborrheic areas with less frequent involvement of the oral mucosa. Oral manifestations, if present, are usually asymptomatic, and are discovered in routine dental examination. Acantholysis and dyskeratosis represented by corps ronds and corps grains are the typical histological findings.

We report a case with clinical signs of DD in the palatal mucosa and skin. Skin biopsy and analysis of clinical history helped to diagnose DD. We report this case because of its clinical rarity as the prevalence of the disease has been estimated at 1/50,000-1,00,000. This could be a case of sporadic mutation as there was no family history. This case emphasizes the importance of oral examination among dermatologists, clinicians and pathologists to clinch the diagnosis of DD as it has a wide range of clinical presentations, therefore going undiagnosed for many years.

**Keywords:** Seborrheic areas, Cobblestone appearance, Corps ronds and corps grains, Sporadic mutation.

## INTRODUCTION

Darier's disease (DD) also known as Darier-White disease or keratosis follicularis, is a rare inherited skin condition with autosomal dominant transmission. It has a worldwide distribution and has an estimated prevalence between 1/50,000 and 1/1,00,000 most often affecting males.<sup>1</sup> The disease is occasionally sporadic and develops from spontaneous mutations in the gene recently identified on chromosome 12 (12q23-q24.1).<sup>2</sup> The pathogenesis of the disease is unknown, but abnormalities of structural proteins may underline the deficiency.<sup>3</sup>

The manifestations of DD appear in childhood and adolescence. The clinical signs are represented by scaly, crusted papules typically occurring on seborrheic areas. Mucous membrane and nail changes also occur.<sup>3</sup>

DD was initially described by Prince Marrow in 1886 and simultaneously by Darier and White in 1889, independently. The first report of mucosal manifestations was described by Reenstierna in 1917. The oral mucosa is affected in 50% of cases; in these cases, lesions are usually asymptomatic and discovered during routine dental examination.<sup>1</sup> Oral mucosal findings include cobblestone appearance of the buccal mucosa and leukoplakia.<sup>3</sup> Acantholysis and dyskeratosis represented by corps ronds and corps grains are the typical histological findings.<sup>1</sup>

This paper reports a case of a patient with DD due to its clinical rarity in dentistry.

## CASE REPORT

A 15-year-old boy presented with itchy skin eruptions at our MS Ramaiah Hospital, Dermatology Department. History elicited from the patient revealed that he had been suffering

from skin eruptions since 3 years and was an outdoor worker. The lesions often worsened during summer. Personal history revealed no tobacco or alcohol habits. The patient had no significant family history or systemic problems.

Physical examination revealed skin lesions on the trunk (Fig. 1), face and extremities. The disease initially started as tiny skin colored papular eruptions on the back which gradually progressed to involve other areas with a dirty greasy crust. Furthermore, careful examination revealed longitudinal streaks and V-shaped nicks at the free edges of his finger nails (Fig. 2).

An incidental oral finding included involvement of the palatal mucosa, presenting a cobblestone appearance (Fig. 3). Thus, an opinion regarding oral involvement was taken from me. Thorough oral examination revealed mucosal alterations only on the hard palate with the presence of multiple asymptomatic coalesced papules with rough texture and hard on palpation.

The patient neither wore prostheses nor presented signs of inflammation. Skin biopsy from the trunk was performed in the most accessible area by the dermatologists and referred to the pathologists for a diagnosis; Thus an oral biopsy was avoided to prevent further discomfort to the patient.

Dermatohistopathology revealed acanthosis, papillomatosis and marked hyperkeratosis with parakeratosis associated with corps ronds and grains. There was suprabasal acantholysis with the formation of suprabasal clefts (Figs 4 and 5). Another prominent finding was the irregular upward proliferation into the clefts of papillae lined with a single layer of basal cells, the so-called villi (Fig. 6). The dermis showed a chronic inflammatory infiltrate. These features confirmed the diagnosis of DD.

Microscopic confirmation with clinical history and skin alterations allowed the clinical-histopathological diagnosis of



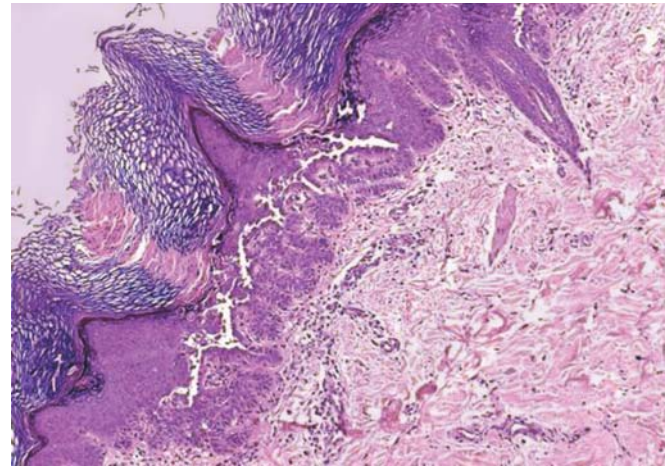
**Fig. 1:** Bilateral distribution of dirty greasy crusted papules at the back and trunk



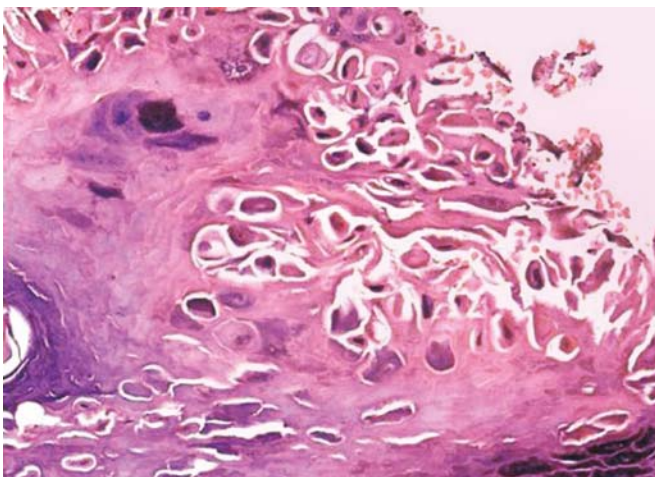
**Fig. 2:** V-shaped nicking at the free edges of finger nails along with longitudinal streaks



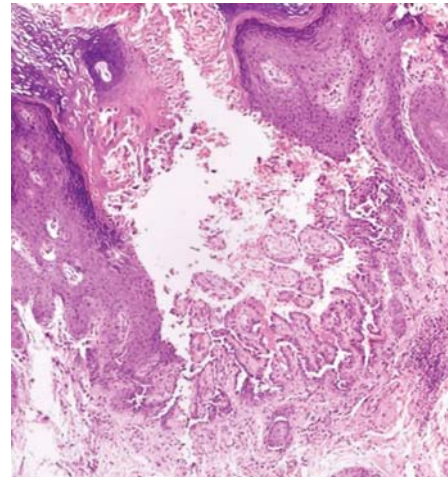
**Fig. 3:** Palatal mucosa presenting with cobblestone appearance



**Fig. 4:** H & E stained section of skin biopsy showing acanthosis, papillomatosis, hyperkeratosis, suprabasal cleft and acantholysis under 10x



**Fig. 5:** H & E stained section showing epidermis with corps ronds in the stratum corneum under 40x



**Fig. 6:** H & E stained section of dermis showing irregular upward proliferation of papillae lined by a single layer of basal cells (villi) under 10x

DD by the multidisciplinary team. The patient is being followed up since then for evaluation of oral and skin alterations.

Isotretinoin (Accutane, Roche) 40 mg twice daily along with 6% salicylic acid and warm water soaks were advised. The patient was monitored for downward adjustments of Isotretinoin. Mouth rinse with antiseptic solutions was prescribed for oral hygiene and utilization of sunscreen was indicated to prevent exacerbation of the skin lesions.

## DISCUSSION

Beyond the genetic inheritance, little is understood about the pathogenesis of DD. More recently, it has been related to mutations in the gene encoding the sarco/endoplasmic reticulum  $Ca^{2+}$  ATPase pump (SERCA2), resulting in abnormal organization or maturation of complexes responsible for cell adhesion, thus leading to the disturbance.<sup>4</sup>

DD has an autosomal dominant inheritance pattern. However, this case showed no family history, which likely indicates a sporadic mutation. This is well-supported that variety of mis-sense, nonsense, frame shift and splicing mutations result in abnormal expression of protein.<sup>4</sup>

DD most commonly manifests from age 6 to 20 years as pruritic lesions involving seborrheic areas. Heat, sweat, humidity, sunlight, UVB exposure, lithium, oral corticosteroids and mechanical trauma have been reported to exacerbate DD.<sup>5</sup> The clinical aspects reported in the present case match those mentioned in the literature.

Nail changes were diagnostic of DD in the present case. Mucosal lesions although uncommon, are detected in approximately 13 to 50%. Oral involvement possibly parallels the severity of the cutaneous disease. The lesions consist of whitish papules of varying size with a central depression or with cobblestone appearance.

Intraoral lesions primarily affect the hard palate and alveolar mucosa, and secondarily the oral mucosa and tongue.<sup>6</sup> In our case, only the palatal mucosa was involved with the typical cobblestone appearance.

Macleod et al in 1991 investigated the incidence and distribution of oral lesions in 24 patients with DD, among whom only 50% had oral manifestations. The palate was the most affected area in his study, followed by the gingiva, oral mucosa and tongue, with varying severity usually following the skin signs. Ferris et al in 1990 observed that 30% of patients presented intermittent sialadenitis of the parotid glands, which is a rare condition first described in the literature by Spouge in 1966.<sup>1</sup>

Clinical variants of DD include hypertrophic and vesicobullous types. Linear or segmental DD accounting for 10% of cases has been shown to result from genetic mosaicism of ATP2A2.<sup>7</sup>

Clinically, moderate forms of the disease are similar to nicotine stomatitis and severe forms are similar to inflammatory fibrous hyperplasia. Thus, smokers and individuals wearing complete dentures should undergo biopsy for a definite

diagnosis. Warty dyskeratoma is histologically similar to DD; however, this is a rare and isolated lesion that affects only mucosa or only skin, thus being classified as an isolated form of DD by some authors.<sup>1</sup>

Skin biopsy is often helpful in confirming the diagnosis of DD. The histopathological characteristics described for the present case satisfied the diagnosis established for DD. Hedblad et al in 1991 and Ruiz-Perez et al in 1999 suggested that DD is not a disorder of keratinization but a disruption of the desmosomal junction, resulting in adhesion problems and acantholysis. They also suggested that it is a disease of haplo-insufficiency.<sup>4</sup>

Histologically, DD is similar to other acantholytic diseases as Hailey-Hailey disease, Grover's disease and pemphigus vulgaris, with the common finding of suprabasal splits in the epithelium. However, cell necrosis is more frequent in pemphigus vulgaris and rarer in Hailey-Hailey and Darier's diseases. Clinical signs are also different for each disorder.<sup>1</sup>

Psychosocial consequences from the appearance and odor of the lesions constitute the major morbidity of Darier's disease.<sup>8</sup>

Although oral lesions have been reported to have no premalignant potential, an oral squamous cell carcinoma has been described in one patient with DD. However, cutaneous squamous cell carcinoma is a possible, but rare complication of DD, and may be the direct consequence of the gene mutations occurring in these individuals.<sup>6</sup>

Cell-mediated immunity of DD patients with bacterial and viral infections are usually normal, except for a few reports in which defects in cell-mediated immunity have been reported by Burge and Wilkison 1992; Sehgal and Srivastava 2005. An increased susceptibility to herpes simplex infection, Kaposi's varicelliform eruption (Hur et al 1994) and pox virus infections occasionally complicate the chronic course of the disease.<sup>4</sup> Initial misdiagnosis of DD may lead to under treatment of such infections and may lead to fatal outcomes. However, overall, patients with DD have a life expectancy similar to that of the general population.

The oral lesions of DD are asymptomatic and thus do not warrant any specific treatment, however, appropriate preventive advice should be provided to all the patients with DD. Patients should be informed on the complications of this disorder and the care required. The emotional status in more severe cases should be followed by a psychologist; therefore, these patients should be treated by a multidisciplinary team.

## CONCLUSION

DD is rare and potentially disfiguring disease. Many patients suffer concomitant psychiatric disorders secondary to their skin disease. Proper diagnosis and treatment of these patients is crucial to improve their quality of life. Our patient had some of the classic clinical and pathological findings of this disorder. DD has autosomal dominant inheritance pattern. However, this case showed no clear family history of the disorder, which suggests a sporadic mutation.

The oral manifestations of DD are often mild and asymptomatic and do not require any extensive oral specialist care. It is possible that oral squamous cell carcinoma can arise

as a consequence of the disease; hence, an appropriate referral is advisable in cases of any doubt regarding the diagnosis.

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