CASE REPORT

Dowling-degos Disease: A Case Report and Clinicopathological Correlation of a Rare Genodermatosis

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ABSTRACT

Dowling-Degos disease (DDD), also termed reticulate pigmented anomaly of the flexure, is a rare genodermatosis characterized by reticulate pigment macules, typically appearing after puberty. We describe a male patient, age 55, who has hyperpigmented papules and macules over the nape of his neck and flexures. The condition was initially diagnosed as lichen planus pigmentosus and has persisted for the past three years. Family history revealed similar skin conditions in maternal siblings and their mother. Skin biopsy demonstrated epidermal changes consistent with DDD, including filiform down-growth epidermis, thinning of suprapapillary plates, and basal layer hyperpigmentation. We discussed the broad differential diagnoses that mimic this condition. Correlating clinical, pathological, and genetic features is essential for its diagnosis. As this genodermatosis is typically resistant to treatment, specific therapies such as laser treatments have shown promise in managing DDD. This emphasizes the importance of correct diagnosis.
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INTRODUCTION

Dowling-Degos disease (DDD), also known as reticulate pigmented anomaly of the flexure, is a rare inherited genodermatosis in which there are reticulate pigment macules of the flexure. Onset usually takes place in the third or fourth decade of life, following puberty, and progresses gradually (2). DDD is attributed to mutations in genes like *KRT5, POFUT1*, or *POGLUT1*, affecting the epidermis and pigmentation regulation. Less than 50 cases have been documented in the literature. We present a case of DDD diagnosed in our institution.

CASE REPORT

This was a 55-year-old male with a history of hepatitis C and hypertension, as well as a family history of similar skin conditions (Figure 1A). He was also a chronic smoker. He worked as a lorry driver and claimed to be frequently exposed to the sun. He presented with coalescing hyperpigmented macules and occasional papules on the nape of his neck and flexural areas for the past three years (Figure 1B & 1C), which he claimed caused mild itchiness especially when he sweats. He also had dry scaly skin over his face and upper limbs. There were no other abnormal physical findings. The initial clinical diagnosis was lichen planus pigmentosus. His mother and maternal siblings had similar skin conditions, which began after the age of 20. A skin biopsy was taken over the back of his neck.

Grossly, we received a pigmented skin tissue, measured 10 mm × 7 mm × 6 mm with no obvious nodule seen. Histopathologically, the epidermis showed filiform down-growth (antler-like pattern), thinning of the suprapapillary plates, increased pigmentation of the basal layer and occasional dilated pilosebaceous follicles (Figure 1D - 1F). There were no interface dermatitis or basal keratinocytes apoptosis observed. No genetic or mutational analysis was conducted. He was treated with topical tretinoin cream for his skin lesions. However, he was lost to follow-up, and the progression of his condition was unknown.

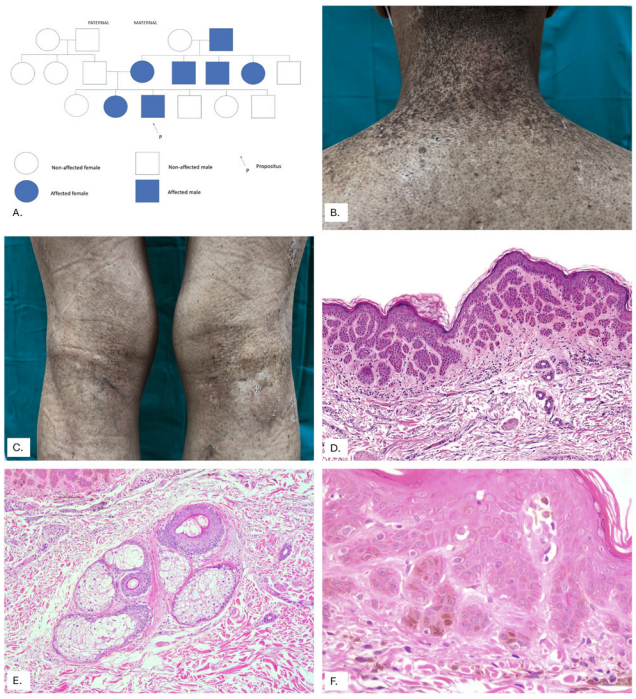

Figure 1: A) This pedigree illustrates the family of the propositus (P), who is an affected male in the third generation. The inherited phenotype is characterized by vertical transmission across three generations, affecting both males and females almost equally. Male-to-male transmission is observed, ruling out X-linked or mitochondrial inheritance. About 50% of the offspring from affected parents are also affected, which aligns with autosomal dominant inheritance. The disease appears in every generation without skipping, suggesting high penetrance. The pedigree shows no evidence of consanguinity. B) Hyperpigmented reticulated macules present at the back of the neck. C) Hyperpigmented macules present at knee flexures. D) Microscopic examination shows filiform epidermal hyperplasia with thinning of the suprapapillary plates accompanied by an increase in basal pigmentation (haematoxylin and eosin [H&E], ×100). E) Mildly dilated pilosebaceous follicles (H&E, ×200) and, F) increase in basal pigmentation are observed (H&E, ×400).

DISCUSSION

First described in 1938, fewer than 100 cases of DDD have been reported in the literature. The condition shows no racial or gender predilection, and lesions typically appear in the third or fourth decade of life (3).

DDD is an uncommon autosomal dominant genodermatosis that is usually resistant to treatment. Mutations in the *KRT5, POFUT1*, or *POGLUT1* gene are responsible for most cases of DDD. The *KRT5* gene produces keratin 5, a protein crucial for maintaining the skin's structure and pigmentation. Keratin 5 helps bind keratinocytes within the epidermis together and transport pigment-carrying structures called melanosomes (5). *POFUT1* and *POGLUT1* genes encode proteins that involve modification of the Notch receptors. These modifications are crucial for proper Notch signaling, which likely plays a role in maintaining melanocyte stem cells and regulating the interactions between melanocytes and keratinocytes within the epidermis (5). In DDD, mutations in the *KRT5* gene reduce the production of functional keratin 5, leading to abnormal epidermis structure and impaired pigment transport. Mutations in *POFUT1* or *POGLUT1* result in dysfunctional proteins, disrupting Notch signaling and potentially affecting keratinocyte and melanocytes interactions (5). The precise mechanisms underlying DDD are still unclear, as its symptoms may stem from impaired Notch signaling or other unknown functions of these proteins in skin cells (5).

Clinically, patients with DDD typically present with hyperpigmentation in flexural areas, occasionally accompanied by pruritus. Physical examination reveals reticulated hyperpigmentation consisting of lentiginous macules and small hyperkeratotic papules in the intertriginous regions. The pigmentation progressively worsens, initially affecting the axillae and inguinal folds, and later spreading to the intergluteal cleft, inframammary folds, neck, trunk, and the medial aspects of the upper arms and thighs. Lesions are rarely found in non-flexural areas (3). Histopathology serves as an important diagnostic tool, revealing a distinct pattern of acanthosis marked by elongated thin rete ridges, often displaying reticulated or fenestrated patterns. Melanin tends to concentrate at the tips of the ridges, and follicular plugging occasionally occurs (1). This reported case exhibits the characteristic features previously described.

The differential diagnoses for reticulate hyperpigmented lesions are broad (Table I). These include dyschromatosis symmetrica hereditaria (DSH), dyschromatosis universalis hereditaria (DUH), and reticulate acropigmentation of Kitamura (RAPK) (1). Despite having distinct pathological features, they share similar clinical phenotypes. There is disagreement regarding whether DDD, DUH, and RAPK are distinct conditions or a range of symptoms associated with a single pigmentary disorder due to the overlap of their clinical features. In the hyperpigmented DSH, the epidermis exhibits increased pigmentation, primarily basal, without elongation of the rete ridges. DUH may show variable epidermal pigmentation, along with some pigment incontinence, mild hyperkeratosis, and sparse perivascular lymphohistiocytic infiltrates (2). The RAPK shows similar pathological features to that of solar lentigo, with club-shaped rete ridge elongations and interspersed epidermal atrophy (2). Other differential diagnosis that caused hyperpigmentation in a reticulated pattern includes Galli-Galli disease, Haber syndrome, confluent and reticulated papillomatosis (CARP), pigmented seborrheic keratosis, acanthosis nigricans, frictional melanosis and erythema ab igne. Infectious causes such as erythrasma, which is caused by *Corynebacterium minutissimum*, can also cause hyperpigmented lesions that commonly occur in flexures.

Table I : Differential diagnosis of Dowling Degos Disease.

Diagnosis	Clinical Features	Pathological Features	Molecular Features/ Aetiology
Dowling-Degos disease (DDD)	Reticulate pigmentation in flexures, comedone-like lesions	Hyperpigmentation of basal layer, epidermal atrophy, elongated rete ridges	AD inheritance pattern, *KRT5, POFUT1* and *POGLUT1* mutations
Reticulate acropigmentation of Kitamura (RAPK)	Reticulate pigmentation on extensor of dorsal hands and feet, skin atrophy	Epidermal atrophy, basilar hyperpigmentation, elongated rete ridges	AD inheritance pattern, *ADAM10* mutation
Dyschromatosis symmetrica hereditaria (DSH)	Hyperpigmented and hypopigmented macules on extremities	Epidermal basilar hyperpigmentation, without elongation of rete ridges.	AD inheritance pattern, *ADAR1* mutation
Dyschromatosis universalis heridataria (DUH)	Hyperpigmented and hypopigmented macules on extremities, face and trunk	Epidermal basilar hyperpigmentation with melanin incontinence	AD and AR inheritance pattern, *ABCB6* mutation
Galli-Galli disease	Similar to DDD with reticulate pigmentation in flexures	Hyperpigmentation with acantholysis	AD inheritance pattern. *KRT5* or *POGLUT1* mutation
Haber syndrome	Reticulate pigmentation, rosacea-like facies, seborrheic dermatitis-like changes, milia	Histological features overlap with DDD, sometimes with follicular plugging	Possibly *KRT5* mutation
Confluent and reticulated papillomatosis (CARP)	Hyperpigmented papules and plaques with peripheral net like configuration.	Acanthosis, papillomatosis, hyperkeratosis and hypergranulosis	No genetic basis. Infectious theory : Caused by *Dietza papillomatosis*.
Erythrasma	Brown-red scaling patches in flexures, coral-red fluorescence under Wood's lamp	Often appears normal in H&E preparation ("invisible dermatosis"). Absence of inflammation. Small coccibacilli on stratum corneum (Gram stain)	Caused by *Corynebacterium minutissimum*
Acanthosis nigricans	Velvety, hyperpigmented plaques in neck, axillae, groin	Hyperkeratosis, papillomatosis, slight acanthosis	Often associated with insulin resistance and diabetes
Pigmented seborrheic keratosis	Well-demarcated, hyperpigmented lesions, often isolated	Basaloid cell hyperplasia, acanthosis, hyperkeratosis, pseudohorn cysts	Somatic mutations of *FGFR3, PIK3CA* or *HRAS* genes
Frictional melanosis	Localized hyperpigmentation in areas of repeated friction or trauma. Often at bony prominences.	Marked diffuse hyperkeratosis with melanin deposits in upper dermis.	No genetic basis, caused by repetitive physical trauma
Erythema Ab Igne	Reticulate pigmentation with fish net pattern due to prolonged heat exposure	Epidermal atrophy, increased melanin, dermal hemosiderin deposits	No genetic basis, caused by heat exposure

This table provides an overview to help differentiate these conditions based on their clinical presentation, pathological features, and molecular features or aetiology. AD: autosomal dominance, AR: autosomal recessive.

Various treatment approaches have been explored in recent years, yet compelling therapeutic outcomes remain elusive. These include depigmenting agents like hydroquinone, systemic retinoids and topical retinoids. Laser therapies, notably Erbium YAG and fractional Erbium YAG, have shown promise in managing DDD (4).

CONCLUSION

DDD, characterized by reticulated pigmentation, presents a diagnostic challenge due to its resemblance to other pigmented skin disorders. Relying solely on clinical appearance may lead to misdiagnosis, underscoring the critical role of histopathological examination in accurately establishing the condition. By analyzing tissue samples, clinicians can discern the distinct histological features, aiding in the precise diagnosis and subsequent management of this rare genodermatosis.

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