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Clinical Case

Reticular Pigmentary Anomalies in Pediatrics

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KEYWORDS

Dowling Degos disease, Gougerot-Carteaud, Acanthosis nigricans, Kitamura disease, Dohi disease, Naegeli-Franceschetti-Jadassohn Syndrome, Galli-Galli disease, Haber Syndrome

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ABSTRACT

Reticular pigmentary anomalies in childhood consists of different entities that clinically present with a common factor of a hyperpigmented reticular skin pattern. This is why they are particularly perplexing for the dermatologist in their daily practice. However, they differ from each other in terms of their age of onset, predominant location, preferred ethnicity, evolution, associated systemic involvement, distinctive histopathological and molecular characteristics, and their therapeutic response. A clinical case about a teenage male diagnosed with Dowling-Degos Disease, evaluated at the Pediatric Dermatology Service of Dr. Ricardo Gutiérrez Children's Hospital is reported as an example.

1. Introduction

Reticular pigmentary anomalies are a group of various described entities that present with characteristic reticular hyperpigmentation of the skin (1). Some of these may be associated with systemic involvement (2, 3). They are often perplexing for dermatologists in their practice, as the case studies are limited for most of them, making clinical differentiation difficult. These conditions exhibit an erratic response to available treatments (4-10). Almost all correspond to genodermatosis, although in the case of acanthosis nigricans, there can occasionally be a significant metabolic trigger in its pathophysiology (2, 3).

Due to their nature as chronic conditions, these have a significant social impact on pediatric patients as they predispose them to difficulties in accepting body image (especially during adolescence), rejection due to their aesthetic appearance, low self-esteem and a higher association with school bullying. In addition, occasionally these entities can be associated with limiting skin involvement, as in the case of those who have suppurative hidradenitis, or with implication of other organs, such as dental anomalies. This further justifies the need for detection to allow for the treatment of possible associated disorders.

The objective of this work is to review and compare the different etiologies, provide useful points for differentiation, and outline diagnostic and therapeutic approaches.

2. Clinical case

A 15-year-old male adolescent, previously healthy with no relevant family history, reports dermatosis of 2 years' duration. Physical examination reveals a reticular hyperpigmented plaque acquired in the anterior cervical region, with scattered macrocomedones, rough to the touch, with well-defined borders, measuring 5x10 cm (Fig. 1, 2). Possible differential diagnoses include: smooth muscle hamartoma, Becker's nevus, and reticular pigmentary anomaly. A biopsy of the cervical region reports: acanthosis, irregular elongation of crest networks, and mild basal hyperpigmentation; slight pigment drop and dilated hair follicles containing debris and keratin, surrounded by bundles of smooth muscle; moderate superficial perivascular linfohistiocytic inflammatory infiltrate, perianexial and comedocytic follicular dilation with mild basal hyperpigmentation. This is compatible with Dowling-Degos disease (Fig. 3). Topical treatment with Adapalene cream at 0.1% and Benzoyl Peroxide gel at 2.5% is initiated. After 4 months, it is supplemented with Dapsone gel at 7.5% with a very good response. Oral Azithromycin cycles at 500 mg per day are started, and photoprotection guidelines are recommended.

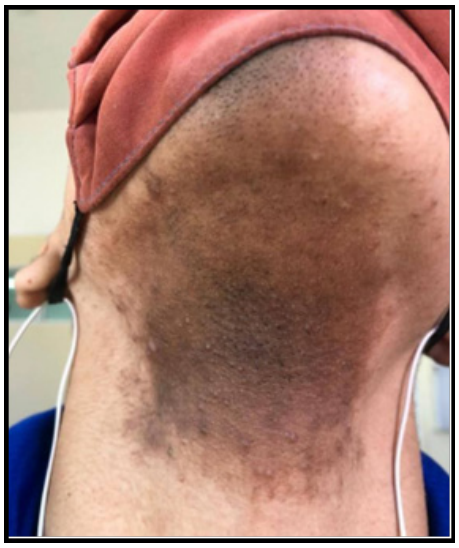

Fig. 1. *In the anterior cervical region: brownish rough plaque with macrocomedones inside.*

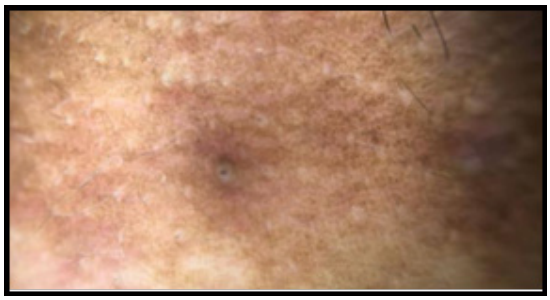

Fig. 2. *At higher magnification, a central macrocomedone is observed with peripheral brownish accentuation.*

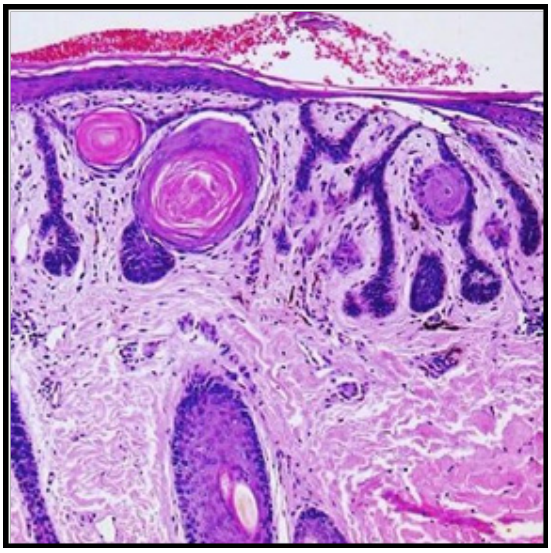

Fig. 3. *HyE at 100X: keratin-filled horn cyst (comedone); thinning of the suprapapillary epidermis; horn-like appearance due to interconnected crest networks; elongated crest networks; pigment loss.*

3. Discussion

A clinical approach to each entity is presented, along with tables of distinctive clinical features (Table I), molecular traits (Table II), histopathological characteristics (Table III), and therapeutic options (Table IV).

Table I. Summary of distinctive clinical features of each entity.

AN	Velvety hyperkeratotic plaques without pits. Onset at any age. Metabolic, syndromic, or hereditary association.
DD	Flexures, confluence. Onset in puberty.
K	Acral pits, early onset.
H	Verruciform papules on the trunk, facial erythema, pinpoint facial scars, early onset.
NFJ	Trunk and extremities, hypohidrosis, palmoplantar hyperkeratosis, and dental alterations.
D	Hypo/hyperpigmented macules on acral dorsal areas, acral atrophy, early onset.
GC	Trunk, scaly or velvety macules. Late onset. Possible hypopigmented lesions in high phototypes.
GG	Lentigines. Constant acantholysis in the basal layer. Late onset – adulthood.

Table II. Molecular features (1, 5, 11-13, 20, 23, 26, 28, 31).

DD	Mutations in KRT5, KRT14, POFUT1, and/or POGLUT1.
GC	Unknown.
K	Mutations in ADAM10.
D	Mutations in ADAR1 and/or ADAM10.
NFJ	Mutations in KRT1 and/or KRT14.
GG	Mutations in KRT5 and/or POGLUT1.
H	Unknown.
AN	Mutations in FGFR3 or INSR.

Table III. Comparative histopathological features (5, 7, 10, 11, 15, 16,18-20 ,26, 29).

DD	Epidermal digitiform proliferations and pilosebaceous follicle, elongation of crest networks, pigment incontinence, moderate hyperkeratosis.
GC	Compact hyperpigmentation, papillomatosis, thinning of the granular layer, epidermal atrophy.
K	Hyperpigmentation of basal keratinocytes, increased melanocytes, elongation of crest networks, epidermal atrophy.
D	Increased basal and epidermal melanin. Hypomelanosis in hypopigmented variants. No melanocytosis.
NFJ	Basal hyperpigmentation, moderate hyperkeratosis.
GG	Acantholysis. Dyskeratosis.
H	Hyperpigmentation of basal keratinocytes with slight elongation of crest networks. Dermal lymphocytic infiltrate.
AN	Dermo-epidermal hyperplasia, orthokeratosis, papillomatosis of the spinous layer, basal layer hyperpimentation without melanocytosis.

Dowling-Degos Disease (DD)

Is an autosomal dominant hereditary condition, infrequent, progressive, and symmetrical. It presents with round macules and papules that can be grayish, brownish, or blackish, asymptomatic, or mildly pruritic (11). They simulate comedones in the axillae, neck, and buttocks (5). Other manifestations include hypopigmentation, perioral pitting, and palmar and acral dorsal involvement (5). There is no internal systemic involvement (5, 11). A clinical-histological correlation is necessary for diagnosis. It has been proposed that follicular occlusion is important in the pathogenesis of the disease, but it is not entirely clear. Mutations of the KRT5 gene, which codes for keratin 5 with loss of function, located on chromosome 12, have been described. This entity shows a fine linear Blaschko pattern, which reinforces the idea that the affected cells are keratinocyte precursors. It is important to mention the activity of the Notch signaling pathway, which determines cellular fate during embryogenesis, aiding the differentiation of the interfollicular epithelium, the hair follicle, and the homeostasis of melanocytes. This

is relevant as mutations have been found in KRT14, POFUT1, and POGLUT1 (the latter two being part of the Notch pathway), affecting melanocytes and their melanosomes, which phenotypically express pigmentary defects (hyper- and hypopigmentation) (11-13).

Gougerot-Carteaud Confluent and Reticular Papillomatosis (GC)

Is a rare chronic condition that presents with exacerbations and remissions (4, 14, 15). It primarily affects women aged 10 to 35 years, with a preference for phototypes IV-V and VI (16). It consists of erythematous-brown papules or small warts forming confluent reticular pigmented plaques, located in the intermamary region, neck, and axillae, later affecting the abdomen, pubis, and face (4, 14-17). Its etiopathogenesis is not yet defined. A genetic or acquired keratinization alteration has been described, which is the most widely accepted theory currently. Additionally, there could be an abnormal host response to fungal antigens from Malassezia furfur and/or bacterial antigens from Propionibacterium acnes, Staphylococcus epidermidis, and Actinomyces Dietzia (15, 16).

Kitamura Reticular Acropigmentation (K)

Is an autosomal dominant and very rare condition (6). It predominates in women in the first 20 years of life (18). It consists of atrophic depressed macules similar to freckles, arranged in a reticular pattern on the acral dorsal area and eventually on the face in the periorbital region (6, 18, 19). It may gradually affect other body areas (6, 18-20). Characteristic findings include palmo-plantar pits and fissures in the dermatoglyphics (18). The mechanism involved is not yet known, although it appears to have similar pathophysiological bases to DD. There are case reports showing a mutation in the ADAM10 gene, which codes for a zinc metalloprotease (12).

Dohi Reticular Acropigmentation (D)

It presents with hyperpigmented and hypopigmented macules in a symmetrical reticular pattern on the dorsal surfaces of the hands and feet, primarily affecting young Japanese patients. It does not present with telangiectasias or atrophy. It is autosomal dominant, although there are reported cases of autosomal recessive and sporadic forms (7, 21, 22). It can extend proximally to the lateral neck and supraclavicular region and face (7, 22). There are case reports of mutations in ADAR1 (adenosine deaminase, RNA-specific) on chromosome 1 and ADAM10, similar to what has been described for K (12).

Naegeli-Franceschetti-Jadassohn Syndrome (NFJ)

Is a rare autosomal dominant syndrome classified among ectodermal dysplasias (8, 23). It presents with partial or total absence of dermatoglyphics, palmoplantar keratoderma, hypohidrosis, reticular hyperpigmentation in skin folds, dental anomalies, and nail dystrophy (8, 23-25). The hyperpigmentation may completely disappear in adulthood. The genes initially implicated code for keratin 1 and are located on chromosome 17q. Recently, the gene that codes for keratin 14 has also been described as a candidate (23).

Galli-Galli Disease (GG)

Is a rare autosomal dominant condition that typically presents between the second and seventh decades of life with confluent hyperkeratotic maculo-papules that later merge to form reticular patches and plaques on the neck, trunk, flexures, and extensions of the limbs. Isolated small macules may be observed in the same described areas (26). Like DD, it can be associated with suppurative hidradenitis (27). It is associated with mutations in keratin 5, which may play a role in the function or transportation of melanosomes (12). Recently, it has also been linked to mutations in POGLUT1 (26).

Haber Syndrome (H)

Is a rare autosomal dominant condition characterized by photosensitive facial erythema similar to rosacea, manifesting in early adolescence, followed by the appearance of reticular hyperpigmentation on the trunk, proximal extremities, and axillae. Other signs include keratotic papules, comedonal lesions, and atrophic depressed scars. Multiple seborrheic keratoses appear during the first decade of life (10).
There have been few reports of this syndrome worldwide. It is not usually associated with mutations in keratin 5, but the spectrum of mutations expected for this entity is still unknown (10).

Acanthosis Nigricans (AN)

It consists of velvety brown plaques primarily in the skin folds of the neck, axillae, and groin (28), occurring in some hereditary, metabolic, and syndromic disorders (2, 3, 28-31). The prevalence is higher in individuals with darker skin (28).
Among its causal agents, we can mention:

• Mutations in the fibroblast growth factor receptor 3 (FGFR3): These have been identified as one of the genetic causes of hereditary acanthosis nigricans (AN), especially in early-onset extensive AN. It is known that mutations in this receptor cause various types of skeletal dysplasia that accompany AN, potentially leading to short stature in adulthood (28).

• Insulin resistance: Skin hyperpigmentation with AN is associated with insulin-like receptors in keratinocytes and dermal fibroblasts, and potentially with an estrogen-induced increase in glycosaminoglycan formation (29, 30). Additionally, AN has been found to be a composite marker of complex cardiometabolic risk, which can be a non-invasive, simple, and valuable clinical evaluation tool for public health screening to assess cardiometabolic risk in children (2, 3).

• Diet: Added sugar and servings of starchy foods have been associated with an increased risk of AN. This determines an association between diet and AN in young children (30).

• Mutations in the INSR gene: These lead to rare hereditary syndromes that cause insulin resistance, such as leprechaunism (Donohue syndrome), Rabson-Mendenhall syndrome, and type A insulin resistance (31).

4. Conclusion

Children with reticular pigmentary anomalies present similar skin manifestations, making it important to recognize the distinctive clinical features of each entity, their distribution, age of onset, and syndromic and metabolic associations. All of this will contribute to a clinical diagnosis that may eventually, according to the patient's needs, be accompanied by a histopathological study to support the suspected disease. Molecular studies are, in most of the developed entities, the way to arrive at a definitive diagnosis.

The proposed treatments in the literature are similar for all the pathologies mentioned in this work. However, there are some preferences (based on better therapeutic response) according to each disease. Nevertheless, no medication will offer a resolution of the case, as they all have a chronic and persistent evolution throughout life. Sun protection is of vital importance and should be promoted to prevent both worsening and exacerbation of the various mentioned conditions.

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All authors report no conflict of interest.

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