

## CASE REPORT

### Dowling–Degos disease

E. F. GEORGESCU<sup>1)</sup>, LIGIA STĂNESCU<sup>2)</sup>,  
CARMEN FLORINA POPESCU<sup>3)</sup>,  
MARIA COMĂNESCU<sup>4)</sup>, IULIANA GEORGESCU<sup>5)</sup>

<sup>1)</sup>*Department of Internal Medicine,  
University of Medicine and Pharmacy of Craiova*

<sup>2)</sup>*Pediatric Clinic,  
"Filantropia" Hospital, Craiova*

<sup>3)</sup>*Department of Pathology and Cytopathology,  
Emergency County Hospital, Craiova*

<sup>4)</sup>*Department of Pathology,  
University Emergency Hospital, Bucharest*

<sup>5)</sup>*Division of Dermatology,  
"Mediplus Diagnostica" Clinical Center, Craiova*

#### Abstract

Dowling–Degos disease (DDD) is a rare autosomal dominant inherited pigmentary disorder of the flexures with a reticulate aspect and with presence of prominent comedone-like lesions and pitted scars. The diagnosis includes acanthosis nigricans as well as other reticulate pigmentary disorders classified into: dyschromatosis symmetrica hereditaria (DSH), dyschromatosis universalis hereditaria (DUH) and reticulate acropigmentation of Kitamura (RAPK). We present a 35-year-old woman, which presented with flexural hyperpigmentation considerate as acanthosis nigricans. At a close clinical and histopathological examination, we obtained sure data for Dowling–Degos disease, with a possible familial history of this disease in her son. We review the literature data concerning this disease.

**Keywords:** Dowling–Degos Disease (DDD), reticulate acropigmentation of Kitamura (RAPK).

#### ☐ Introduction

Dowling–Degos disease (DDD) is a rare autosomal dominant inherited pigmentary disorder characterized by reticulate pigmentation of the flexures, prominent comedone-like lesions and pitted scars [1]. Reticulate hyperpigmentary disorders have been classified into dyschromatosis symmetrica hereditaria (DSH) of Toyama, dyschromatosis universalis hereditaria (DUH), Dowling–Degos disease (DDD) and reticulate acropigmentation of Kitamura (RAPK) [2].

We report a female patient with clinical aspect and histopathology compatible with the diagnosis of DDD with the existence of a familial history in her son. We discuss the possible pigmentary skin disorders concerning the differential diagnosis.

#### ☐ Patient and Methods

A 35-year-old woman demands examination in internal medicine for digestive symptomatology consisted of epigastric pains, nausea and vomiting. The clinical examination at the tegument inspection discovers in the flexural area (axillae, submammary) a hyperpigmentation, which led us to the diagnosis of acanthosis nigricans, dermatose that in adult can be associated with an internal malignity, especially digestive. Therefore, in addition to the laboratory examination it was considered necessary an endoscopic examination. It was concentrated of the history on the

tegumentary aspects and other disease correlated with this. It was demanded a careful dermatological examination and a histopathological one. The latest was realized on the lesional fragments from the different area, fixed in 10% formalin, paraffin-embedded and routinely stained with Hematoxylin–Eosin and van Gieson, examined by light microscopy.

#### ☐ Results

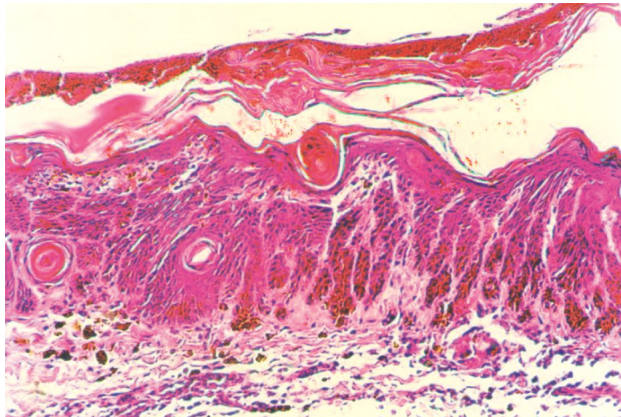
Endoscopical examination showed an eritematous gastritis in the absence of the any sign of the gastric malignity. The history of this cutaneous disease suggested that the onset was around the age of 19 years with a gradually and progressive pigmentation in the axillae, submammary folds and neck. She affirmed that the flat pigmented lesions appeared first in the axillae, the pigmentation grow gradually in intensity during similar lesions invade slowly other areas. She observed the slowly apparition on the decolletage, back, especially on the neck, then on the face around the eyes and perioral of a punctiform lesions, prominent which leave pitted scars. It is important to remark that her unique son present similar pigmentary lesions in the axillae folds from the age of 14 years. These lesions were discovered accidentally when he was examined for another medical reason. His son could not be examined when he was in treatment for another disease. Other relatives of the patient have

not presented such cutaneous manifestations.

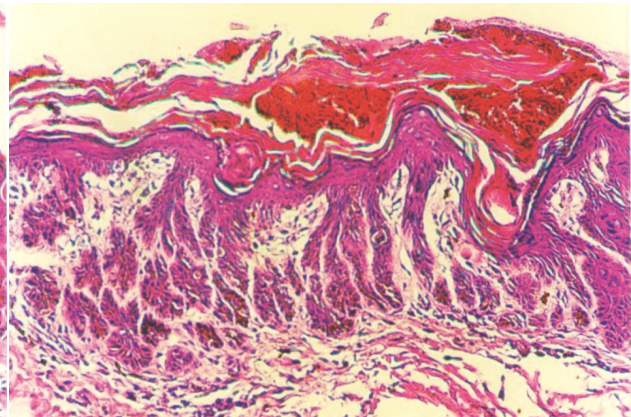
The dermatological examination shows deep brown reticular pigmentation in axillae, submammary folds in the groins and on the face and neck, especially perioral. The pigmentation consists of numerous small, discrete rounds to oval pigmented macules, with reticulate distribution. This is symmetrical localized and completely asymptomatic. On the face, especially on the neck and perioral it observed multiple comedones and pitted scars. Also on the neck and back are present numerous hyperkeratotic comedone-like dark brown follicular papules and pitted scars. Palms, soles, nail and mucous membrane was normal. The histopathological exami-

nation on the tegumentary fragments from the cutaneous pigmented lesions in the right axial and the dorsal part of the neck discovers the following images:

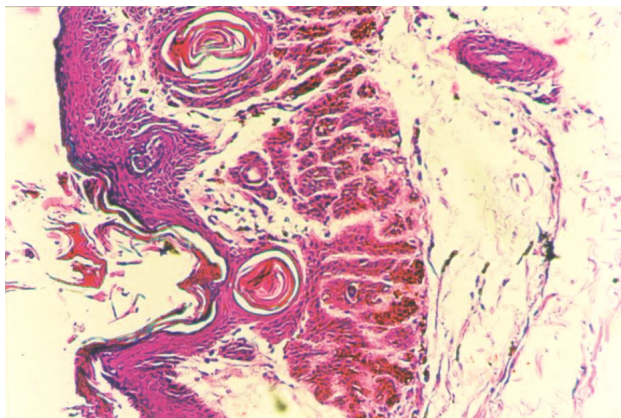
- the increased pigmentation of the basal layer with hyperplasia of the melanocytes and with filiform epithelial down growths arising from the epidermis (Figures 1 and 2); thinning of the epidermis immediately above these down growths and presence of keratotic plugs in some areas (Figure 3); areas of hyperplasia and cystic transformation of sweat glands (Figures 4 and 5); dermal fibrosis (Figure 6); perivascular lymphohistiocytic infiltrate within the derma (Figures 7 and 8).



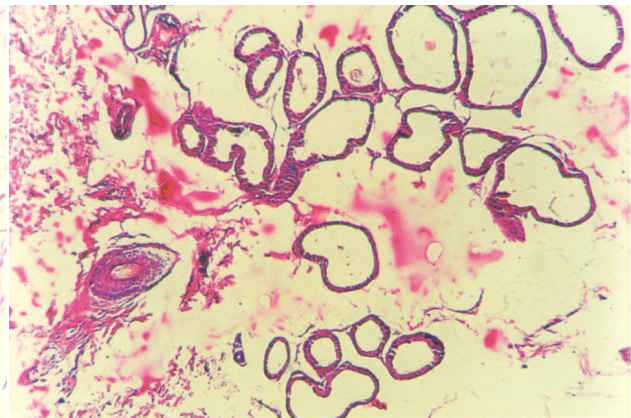
**Figure 1 – Epidermis with increased pigmentation of the basal layer and with filiform epithelial growths into the dermis (HE stain,  $\times 100$ ).**



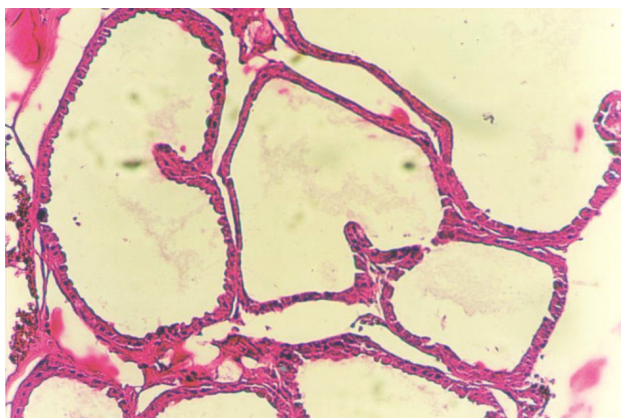
**Figure 2 – Atrophic epidermis with pattern out-ridges of the epidermal ridges and hyperpigmentation of the basal layer (HE stain,  $\times 100$ ).**



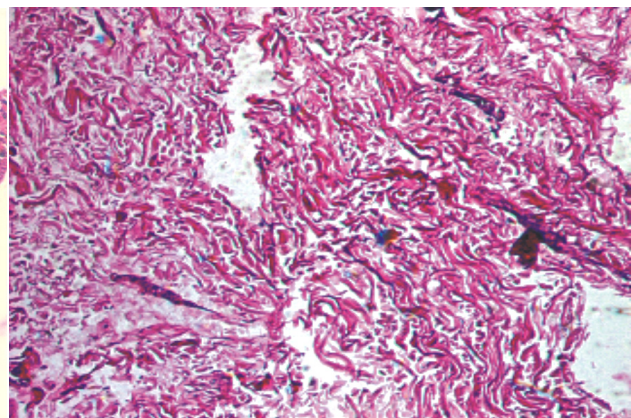
**Figure 3 – Epidermis with atrophic and acanthotic areas; keratotic plugs in some areas (HE stain,  $\times 100$ ).**



**Figure 4 – Areas of hyperplasia and microcystic transformation of the sweat glands (HE stain,  $\times 100$ ).**

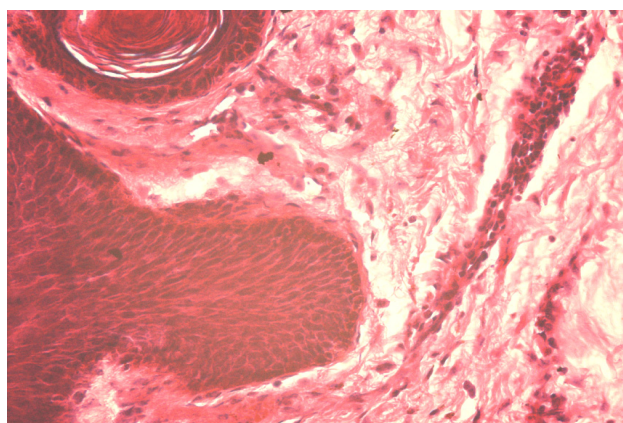


**Figure 5 – Areas of cystic transformation of the sweat glands (HE stain,  $\times 200$ ).**

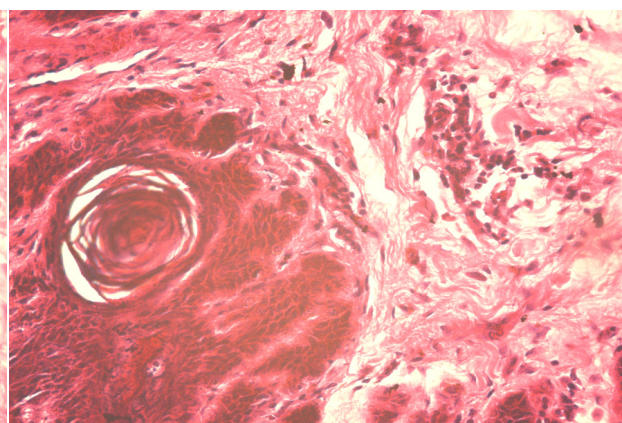


**Figure 6 – Deeper dermis with dens fibrosis (HE stain,  $\times 100$ ).**





**Figure 7** – Perivascular lympho-histiocytic infiltrate within the superficial derma (HE stain, ×200).



**Figure 8** – Perivascular lympho-histiocytic infiltrate within the superficial derma (HE stain, ×200).

## Discussion

Dowling–Degos disease (DDD) is an autosomal dominant genodermatosis characterized by reticulate pigmentation of the flexures. This rare genodermatosis was first described by Dowling GB and Freudenthal W in 1938 as a benign form of acanthosis nigricans [3], subsequent, she was termed “dermatose reticulée des plis” by Degos R and Ossipowski B in 1954 [4]. DDD was first characterized by Wilson-Jones and Grice in 1978 in their description of 10 patients with the disorder and recognized as a distinct entity [5]. It is an autosomal dominant inherited pigmentary disorder [6] usually of adult onset, in individuals before they are aged 24 years, but may occur in childhood [1]. A Chinese newborn with reticulate pigmented anomaly of the flexures was recently described [7].

The disease affects both sexes, although, a female predominance has been noted in some surveys [8].

DDD is often familial and appears to be inherited in an autosomal dominant manner [9]. Recently, a gene locus believed responsible in one Chinese patient was mapped to 17p 13.3 [10] and a genome-wide linkage analysis of two German families describe localization of the first DDD locus on chromosome 12q/8/A [11]. This region includes the keratin gene cluster, which was screened for mutations. Loss of function mutations were identified in the keratin 5 gene (KRT 5) in all affected family members and in six unrelated patients with DDD. Keratin 5 is a component of the intermediate filament (IF) cytoskeleton in the basal layer of the keratinocytes [11]. Dysfunction of the IF cytoskeleton causes aberrant distribution of melanomes degradation suggesting a delayed degradation of melanin granules [11].

Thus, in a family with DDD, a heterozygous frame-shift mutation in the V1-domain of keratin 5 was identified [12]. These data confirm that haplo-insufficiency for K5 causes DDD and points to a prominent role for the keratin intermediate filament cytoskeleton within basal keratinocytes in epidermal pigment biology. Clinical manifestations of DDD or reticulate pigmented anomaly of the flexures (RPAF) are dominated by spotted and reticulate pigmentation of the flexures [5, 6] which may be associated with dark comedone-like lesions and pitted scars.

The pigmentation is progressive, symmetrical, often extensive and completely asymptomatic [1]. This most commonly affects the axillae, groins, submammary folds and neck, but sometimes can spread to involve the face, chest, perineum, natal clefts and wrists [13, 14]. The pigmentation consists of numerous small, discrete round to oval pigmented macules which resemble freckles. It may be intense, with a brownish black color and sometimes steel blue or navy overtones. However, if the condition is less severe, it is stippled in shades of brown [15]. In many of these disorders, they are freckle-like and angulated and tend to join at their margins to form a reticulate pattern. The confluence of lesions toward the vault of the axillae and the centre of genitocrural folds was observed by Sandhu K *et al.* [1]. If the patches are palpable, it is because of lichenification that produces a glossy and at times somewhat wrinkled appearance.

The pigmentation undergoes slow growth over the years and worsens in summer [5, 6, 14].

Other common features includes; hyperkeratotic comedone-like dark-brown follicular papules on the back and/or neck; pitted scars most characteristically occur around the lateral margins of the mouth, but can involve other areas of the face, neck, axilla, thighs, etc [1]; pruritus on the affected areas. In addition, speckled macules involving the dorsum of the hands, the proximal nail folds, or the scrotum [15] may be seen. Finger-nail dystrophy may be present, particularly finger-like fibroma [8, 16]. The finding of speckled macules on the scrotum is isolated and limited to the scrotal and penile skin [15]. This pigmented eruption on the male external genitalia is possibly a cutaneous marker of underlying testicular carcinoma. In female patients, speckled macules may be found on the vulva [17, 18].

Various affections have been associated with this disease. Thus, the association of DDD and hidradenitis suppurativa (HS) [19] single or associated with other disease as well as multiple keratoacanthomas [20], multiple epidermal cysts [21] and perianal squamous cell carcinoma [22], multiple seborrheic warts is well reported. The association of pigmented eruption on the male external genital has been considered as a possible marker of underlying testicular carcinoma [15], although the association is probably fortuitous. Concerning HS,

it is thought that they could be due to clinical manifestation of a single underlying defect in follicular keratinization. Identically, for the same of the other conditions, their coexistence in the same patient is likely to reflect the same follicular anomaly. It is possibly that a single underlying defect of follicular proliferation may account for the coexistence of these conditions.

Histological, the affected skin shows elongated epidermal rete ridges with thinning of the suprapapillary epithelium and basilar hyperpigmentation in a filiform pattern. Perivascular lympho-histiocytic dermal infiltration and dermal fibrosis along elongated rete ridges are observed [8]. Also, intra-epidermal keratin cysts may be remarked [16]. Occasionally, hamartomatous epidermal changes have been identified [16, 22]. The downward elongation is composed of regular pigmented basaloid cells. An increased number of melanophages has been observed in, with no quantitative increase in the number of melanocytes [5].

In a latest study, all pigmented cells in the basal layer were recognized by anti-PEP-1, anti-PEP-2, HMB-45 and NK1/beteb antibodies. The melanocytes were localized in the basal layer and accounted for 10% of the total keratinocytes. Supranuclear "caps" of brown granules were observed within most basal keratinocytes in the hyperpigmentation area. The melanocytes contained many mitochondria, Golgi apparatus, and regular melanosomes in all stages of maturation in their cytoplasm; melanosome-laden dendrites were readily detected by transmission electron microscope. Melanosomes mainly of stages III and IV were evident within keratinocytes either distributed as scattered patterns or forming "caps" over the nucleus [23].

Differential diagnoses include acanthosis nigricans and other human genetic pigmental disease, such as reticulate acropigmentation of Kitamura (RAPK), dyschromatosis symmetrica hereditaria (DSH), dyschromatosis universalis hereditaria (DUH).

In acanthosis nigricans, the plaques are velvety and there may be skin tags but no dark comedone-like lesions. Histologically, there is papillomatosis in acanthosis nigricans and no follicular anomalies.

The onset of RAPK is in the first two decades of life. The location of macules is acral rather than flexural. There are palmar and plantar pits and breaks in the epidermal ridge pattern, which were not found in this patient. The histological features of DDD and RAPK are however, very similar; RAPK lacking only the antler-like pattern of the epithelial proliferation. Several authors reported that Dowling–Degos disease and RAPK might be different clinical expressions of the same disease [10].

DSH is an autosomal dominant inheritance characterized by pinpoint, pea-sized, hyperpigmented, and hypopigmented macules limited largely to the dorsal aspects of the hand and feet [24].

DDD are dominated by spotted and reticulate pigmentation of the flexures. In addition, the gene for DSH has previously been mapped to chromosome 1q11–1q21 [25], in which the RNA-specific adenosine deaminase gene was identified as the disease gene for DSH [10, 24, 26].

Dyschromatosis universalis hereditaria is characterized by pigmented flecks and spots over much of the body other than that limited to the flexures of body [26]. In addition, the gene for dyschromatosis universalis hereditaria has previously been mapped to chromosome 6q24.2–q25.2 [26].

DDD exhibits a slow progressive course. Treatment of DDD is complicated, usually with poor results. Transient good results have been reported with the use of topical corticosteroids, depigmenting agents, topical adapalene and Er: YAG laser pulse energy between 1000 and 1200 mJ, three consecutive passes [27, 28]. These treatments led to a good clinical result and might be a successful strategy in DDD.

## Conclusions

The clinical aspects and the histopathological examination discovered in our patient are correlated with the diagnosis of DDD, with possible familial history in her son. Treatment of DDD is complicated and usually which poor results. It necessary ample studies on a numerous patients with this rare disease for evaluation the efficacy and safety of the different therapeutically variants.

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### Corresponding author

Eugen Florin Georgescu, Professor, MD, PhD, Department of Internal Medicine, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200349 Craiova, Romania; Phone +40744–782 136, Fax +40251–420 896, e-mail: efg@usa.net

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