Dowling-Degos Disease and Hidradenitis Suppurativa. Epidemiological and Clinical Study of 15 Patients and Review of the Literature

Eugenia AGUT-BUSQUET[1], Iris GONZÁLEZ-VILLANUEVA[2], Jorge ROMANÍ DE GABRIEL[1], Jose Carlos PASCUAL[2], Miquel RIBERA PIBERNAT[1] and Jesús LUELMO[1]

[1]Department of Dermatology, University Hospital Parc Tauli of Sabadell, Autonomous University of Barcelona, Barcelona, Spain, and [2]Department of Dermatology, Alicante University General Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL-FISABIO Foundation), Alicante, Spain. E-mail: eagutbusquet@gmail.com

Accepted May 22, 2019; E-published May 23, 2019

Dowling–Degos disease (DDD), or reticular pigmented anomaly of the flexural surfaces, is a rare autosomal dominant genetic pigmentation disorder (1). DDD occurs more frequently in women and lesion onset is usually after puberty. DDD clinically presents as an acquired dot-like or reticular hyperpigmentation of the skinfolds, depressed pitted scars in the periorbital region and pinpoint papules with keratin plugs in the palmar, axillary, cervical, perioral and gluteal regions, with a characteristic histopathology (2). The differential diagnosis includes acanthosis nigricans, Naegeli-Franceschetti-Jadassohn syndrome, confluent and reticulated papillomatosis, Galli-Galli disease, Haber syndrome, reticulate acropigmentation of Kitamura and Dohi, dyschromatosis symmetrica universalis hereditaria and other dyskeratotic syndromes. In 2006 it was established that mutations in KRT5, POFUT1 and POGLUT1 are implicated in DDD (3, 4).

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory disease with a multifactorial aetiopathogenesis. Abnormalities in the innate immune system promote a maintained high-grade inflammatory state in response to keratin, corneocytes, bacteria and sebaceous material that is extruded when a pilosebaceous unit is disrupted (5).

DDD has been associated with conditions such as infundibular cysts, keratoacanthomas (6) and squamous cell carcinoma (7), while the co-occurrence of DDD with HS has only been reported in 6 unique clinical cases (2, 6–8).

We report epidemiological and clinical characteristics for a cohort of 15 patients with DDD, concomitantly affected by HS, who attended the Dermatology Services of Alicante Hospital and Sabadell Hospital between 2015 and 2017.

MATERIAL AND METHODS AND RESULTS

Approval for the study was obtained. Data gathered from the medical records included epidemiological characteristics, clinical information (including Hurley Stage and International Hidradenitis Suppurativa Severity Score System (IHS4) (9)) and treatment information. Results for categorical variables were expressed as absolute frequencies and percentages. Descriptive statistics for continuous variables were expressed as means ± standard deviations (SD). Statistical tests were carried out using SPSS version 22.0.

The retrospectively reviewed cohort of 15 patients included 8 men (53%) and 7 women (47%). Mean ± SD age was 43.27 ± 12.36 years. All patients reported a family history of HS and 60% reported a family history of DDD. Mean ± SD age of onset for HS was 15.60 ± 3.69 years. Mean age of evolution was 27.67 ± 14.61 years. A history of acne was reported in 7 patients (47%). Metabolic syndrome, hypertension, diabetes mellitus, dyslipidaemia and pilonidal sinus were reported in a minority of patients (27%, 20%, 20%, 27% and 20%, respectively). Smokers accounted for 80% of the patients and 53% of the patients were overweight, with a mean BMI of 27.93.

Clinical exploration revealed the patients to have clinical findings suggestive of DDD (**Fig. 1**). Hair and nails were normal. To confirm the diagnosis of DDD, a punch biopsy was performed in all the patients in either the axilla or the major abdominal flexure (Fig. S1[1]). Active acne, nodules, abscesses and sinus tracts were observed in 46.66%, 100%, 80% and 33.33% of the patients, respectively. The involved body parts were mainly axillae (100%), groin (93%), nape and back (66.66% each) and gluteal and pubic areas (53.33% each). Infundibular cysts (mean count 6.67) were observed in 14 patients. The most common Hurley stage was II (47%). Mean IHS4 was 9.7.

Regarding the management, during the 2 years of follow-up, over half the patients (53%) received more than 2 types of treatment: 46% received rifampicin 300 mg b.i.d plus clindamycin 300 mg b.i.d for 12 weeks, followed by a maintenance therapy consisting of topical application of either a 1% clindamycin solution or a 15% resorcinol solution 3 times a week; while 40% received either sulfone 50 mg b.i.d or acitretin 25 mg q.d; and 13.33% received adalimumab 40 mg/week.

[1]https://doi.org/10.2340/00015555-3225

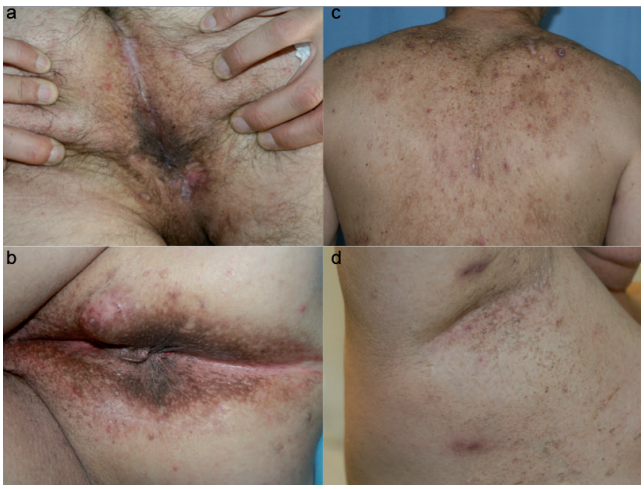

Fig. 1. Clinical images. a) Patient #13. Symmetrically distributed hyperpigmented macules with a reticular disposition affecting the perineal area. Note the 2 nodules and the non-draining fistula. b) Patient #13. Comedon-like infundibular cysts and follicular plugging. c) Patient #14. Typical DDD hyperpigmented macules in major skinfolds. Note the inflamed abscess in the perineal area. d) Patient #14. Note the non-inflammatory nodules in the right axillae, hyperpigmentation and multiple double-comedon openings.

doi: 10.2340/00015555-3225
Acta Derm Venereol 2019; 99: 917–918

DISCUSSION

Different proposals for phenotypic HS classification have tried to group patients according to common clinical findings. Canoui-Poitrine et al. (10) described 3 phenotypes based on latent class analysis (LCA): LCA-I or axillary-mammary (overweight women, lesions in the axillae and the inframammary areas), LCA-II or follicular (normal-weight men, history of acne, severe follicular disease involving the trunk), and LCA-III or gluteal (less frequently obese, less severe than LCA-II, involving the gluteal area). Frew et al. (11) simplified this classification into typical and atypical HS, pointing out that LCA-I patients correspond to the typical HS group, whereas LCA-II and LCA-III patients correspond to the atypical HS group. The atypical category includes normal-BMI men with a follicular pattern of HS, a family history and possibly a high genetic risk profile. Further subtypes – including the conglobata, ectopic and syndromic subtypes – have been proposed by Van der Zee & Jemec (12), who points out that some patients with atypical HS have severe scarring and underlying genetic alterations. The patients in our series fit mostly into the atypical subgroup, characterized by a family history of HS, a current history of acne and trunk involvement. It is noteworthy that the nape involvement – a finding that is uncommon in typical HS – was observed in more than half of our patients. Recently, nape involvement in patients with HS has also been described as an association with DDD (13). However, certain characteristics of our patients – excess weight, involvement of the groin and axillae and a high prevalence of abscess formation – would indicate that they match better with the typical HS group.

In 2015, Wang (14) found that nicastrin and presenilin-enhancer mutations occurred more frequently in young men with lesions in the nape area. They suggested that mutations in the gamma-secretase inhibitors of the NOTCH signalling pathway led to epidermal and follicular abnormalities, with consequent cystic hyperkeratosis and epidermal cyst formation – both clinical findings for our series of patients. Since 2006, *KRT5*, *POFUT1* and *POGLUT1* have been identified as the causative genes for DDD (3, 4, 15). Patients with features of DDD who are negative for *KRT5* mutations are likely to harbour mutations in either *POGLUT1* or *POFUT1*. The fact that both *POFUT1* and *POGLUT1* are essential regulators of the NOTCH signalling pathway highlights the importance of this pathway in pigmentation and epidermal differentiation (5). For one patient in our series, a new mutation in the *POFUT1* gene has recently been described (15). The above findings support the idea that mutations in the γ-secretase inhibitors may underlie the concomitant development of HS and DDD.

Considering that these patients have numerous epidermal cysts, retinoids and sulfone are used, although they frequently fail to maintain clinical stability. Biologic treatment is available for patients who fail to respond. Due to the increased risk of skin malignancies, long-term follow-up of patients with DDD and HS is crucial.

To our knowledge our cohort is the largest one described where patients concomitantly affected by DDD and HS and featured by early age of onset, a family history of DDD or HS and a remarkably high number of infundibular cysts.

ACKNOWLEDGEMENTS

This article forms part of a PhD Programme at the Autonomous University of Barcelona (UAB).

The authors have no conflicts of interest to declare.

REFERENCES

1. Dowling GD, Freudenthal W. Acanthosis nigricans. Proc R Soc Med 1938; 31:1147–1150.
2. Bedlow AJ, Mortimer PS. Dowling-Degos disease associated with hidradenitis suppurativa. Clin Exp Dermatol 1996; 21: 305–306.
3. Betz RC, Planko L, Eigelshoven S, Hanneken S, Pasternack SM, Bussow H, et al. Loss-of-function mutations in the keratin 5 gene lead to Dowling-Degos disease. Am J Hum Genet 2006; 78: 510–519.
4. Basmanav FB, Oprisoreanu AM, Pasternack SM, Thiele H, Fritz G, Wenzel J et al. Mutations in POGLUT1, encoding protein O-glucosyltransferase 1, cause autosomal- dominant Dowling-Degos disease. Am J Hum Genet 2014; 94: 135–143.
5. Kelly G, Sweeney CM, Tobin AM, Kirby B. Hidradenitis suppurativa: the role of immune dysregulation. Int J Dermatol 2014; 53: 1186–1196.
6. Loo WJ, Rytina E, Todd PM. Hidradenitis suppurativa, Dowling-Degos and multiple epidermal cysts: A new follicular occlusion triad. Clin Exp Dermatol 2004; 29: 622–624.
7. Li M, Hunt MJ, Commens CA. Hidradenitis suppurativa, Dowling Degos disease and perianal squamous cell carcinoma. Australas J Dermatol 1997;38: 209–211.
8. Arjona-Aguilera C, Linares-Barrios M, Albarrán-Planelles C, Jiménez-Gallo D. Enfermedad de Dowling-Degos: caso clínico asociado a hidradenitis supurativa. Actas Dermosifiliogr 2015; 106: 337–338.
9. Zouboulis CC, Tzellos T, Kyrgidis A, Jemec GBE, Bechara FG, Giamarellos-Bourboulis EJ, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. Br J Dermatol 2017; 177: 1401–1409.
10. Canoui-Poitrine F, Le Thuaut A, Revuz JE, Viallette C, Gabison G, Poli F, et al. Identification of three hidradenitis suppurativa phenotypes: latent class analysis of a cross-sectional study. J Inv Dermatol 2013; 133: 1506–1011.
11. Frew JW, Vekic DA, Woods J, Cains GD. Phenotypic heterogeneity implies heterogeneous pathogenic pathways in hidradenitis suppurativa. Exp Dermatol 2015; 24: 338–339.
12. Van der Zee HH, Jemec GB. New insights into the diagnosis of hidradenitis suppurativa: Clinical presentations and phenotypes. J Am Acad Dermatol 2015; 73: S23–26.
13. Agut-Busquet E, Romaní J, Ribera M, Luelmo J. Hidradenitis suppurativa of the nape: description of an atypical phenotype related to severe early-onset disease in men. J Dermatol 2019; 46: 149–153.
14. Wang B. γ-Secretase mutation and consequently immune reaction involved in pathogenesis of acne inversa. J Investig Dermatol Symp Proc 2015; 17: 25.
15. Gonzalez-Villanueva I, Gutierrez M, Hispan P, Betlloch I, Pascual JC. Novel POFUT1 mutation associated with hidradenitis suppurativa-Dowling-Degos disease firm up a role for Notch signaling in the pathogenesis of this disorder. Br J Dermatol 2018; 178: 984–998.