Actas Dermosifiliogr. 2007;98:425-9

CASE REPORTS

Acral Keratoses and Inverted Follicular Keratosis Presenting as Cowden Disease

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Abstract. Cowden disease is a rare genetic disorder characterized by the presence of multiple hamartomas in the skin, thyroid, breast, nervous system and gastrointestinal tract. Mucocutaneous lesions are the most constant and characteristic finding. Breast and thyroid neoplasms (benign and malignant) develop in up to two thirds of patients. Inverted follicular keratosis as the presenting feature of Cowden disease is rare as the disease is usually suspected by the appearance of multiple facial trichilemmomas, oral mucosal papillomatosis and acral keratoses.

Key words: Cowden disease, inverted follicular keratosis.

QUERATOSIS ACRAS Y QUERATOSIS FOLICULAR INVERTIDA COMO MANIFESTACIÓN DE LA ENFERMEDAD DE COWDEN

Resumen. La enfermedad de Cowden es un trastorno genético poco frecuente caracterizado por la presencia de múltiples tumores hamartomatosos en piel, tiroides, mama, sistema nervioso y tracto gastrointestinal. Las lesiones mucocutáneas son el hallazgo más constante y característico. Las neoplasias (tanto benignas como malignas) de la mama y del tiroides aparecen hasta en dos tercios de los pacientes.

La queratosis folicular invertida como forma de presentación de una enfermedad de Cowden es rara, ya que suelen ser los triquilemomas faciales múltiples, las lesiones papilomatosas de la mucosa oral y las queratosis acras la que suelen hacer sospechar esta enfermedad.

Palabras clave: enfermedad de Cowden, queratosis folicular invertida.

Introduction

Cowden disease is a genodermatosis that presents ectodermal, endodermal, and mesodermal abnormalities. It is an autosomal dominant inherited disease and affects both sexes, though it is somewhat more common in women. The prevalence is of 1 case per 200 000 healthy individuals.[1] Cowden disease is caused by a germline mutation in the *PTEN* gene.[2] The skin findings, which develop in 90% of patients, consist of trichilemmomas, acral keratoses, oral papilloma, and sclerotic fibroma. The extracutaneous features of Cowden disease include the presence of lesions in the thyroid (goiter, adenomas, thyroglossal cysts, and follicular adenocarcinoma) and breast (fibrocystic disease, fibroadenoma, and breast cancer), and the possibility of developing gastrointestinal, genitourinary, utero-ovarian, cerebral, and skeletal manifestations.

We present the case of a patient with Cowden disease in whom the principal cutaneous manifestations that led us to suspect this disease were acral keratoses and inverted follicular keratosis.

Case Description

The patient was a 60-year-old woman who had previously been treated surgically for right-sided breast cancer (1997), endometrial adenocarcinoma (1998), and multinodular goiter (2002), and had also been diagnosed with a meningioma of the left sphenoid wing (2004). She attended our outpatient clinic for a second evaluation of asymptomatic skin lesions in the area in which radiotherapy had been performed for the breast cancer (a previous biopsy gave a diagnosis of postmastectomy dermal lymphangioma) and lesions in the axillas and on the scalp (biopsied, with a diagnosis of verruca vulgaris and inverted follicular keratosis). There was no relevant family history.

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Manuscript accepted for publication September 20, 2007.

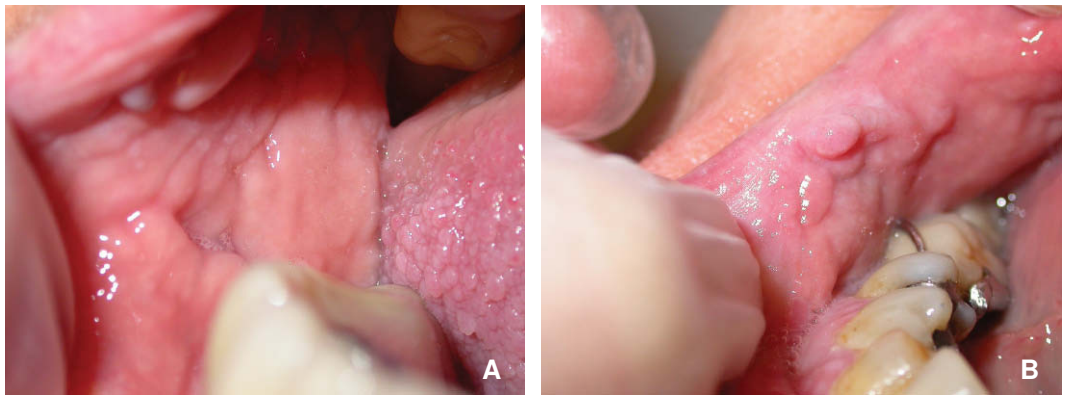

Figure 1A and B. Fleshy papules on the buccal mucosa that are confluent in some areas, producing a cobblestone appearance.

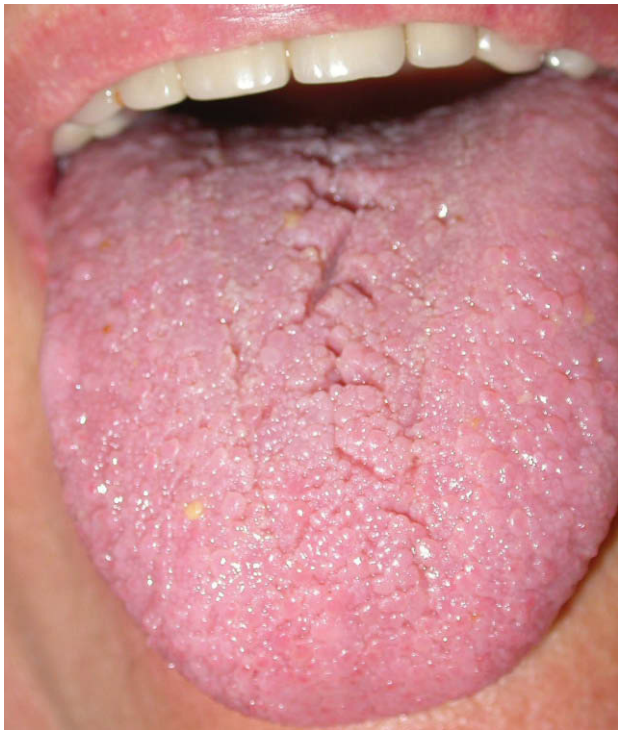

Figure 2. Fissures on the dorsum of the tongue and flesh colored papules on the lateral borders.

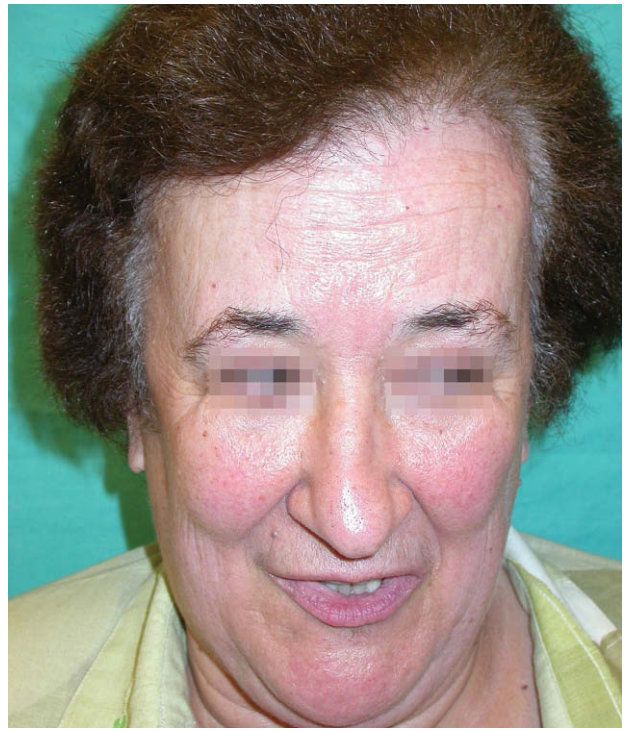

Figure 3. Macrocephaly.

On physical examination, numerous, skin-colored papules of 1 to 3 mm diameter were observed on the buccal mucosa, creating a cobblestone pattern (Figures 1A and B). The tongue presented central sulci and numerous fleshy papules were observed on the lateral borders (Figure 2).

The patient also displayed macrocephaly (Figure 3), a number of keratotic papules on the dorsum of the hands and feet and on the scalp (Figure 4), and multiple lesions in the form of translucent papules of vesicular appearance in the right axilla and right submammary region (Figure 5). There was no eye involvement.

Biopsies of a lesion close to the areola of the breast and a lesion in the area of the right breast resulted in diagnoses of seborrheic keratosis and lymphangioma, respectively.

In addition, we reviewed the scalp biopsy performed previously, in which an epithelium with hyperkeratosis and acanthosis could be observed. At higher magnification, scattered squamous whorls were observed in a squamous epithelium surrounding a hair follicle, together with tortuous, congested capillaries containing abundant red blood cells, compatible with an inverted follicular keratosis (Figures 6A and B).

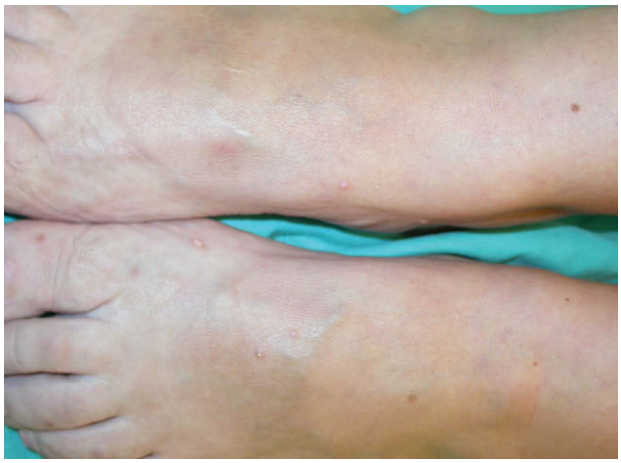

Figure 4. Keratotic papules on the dorsum of the feet.

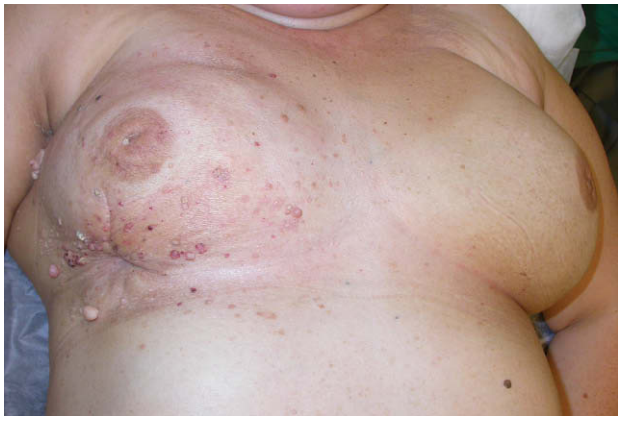

Figure 5. Translucent papules in the area of the right breast and axilla.

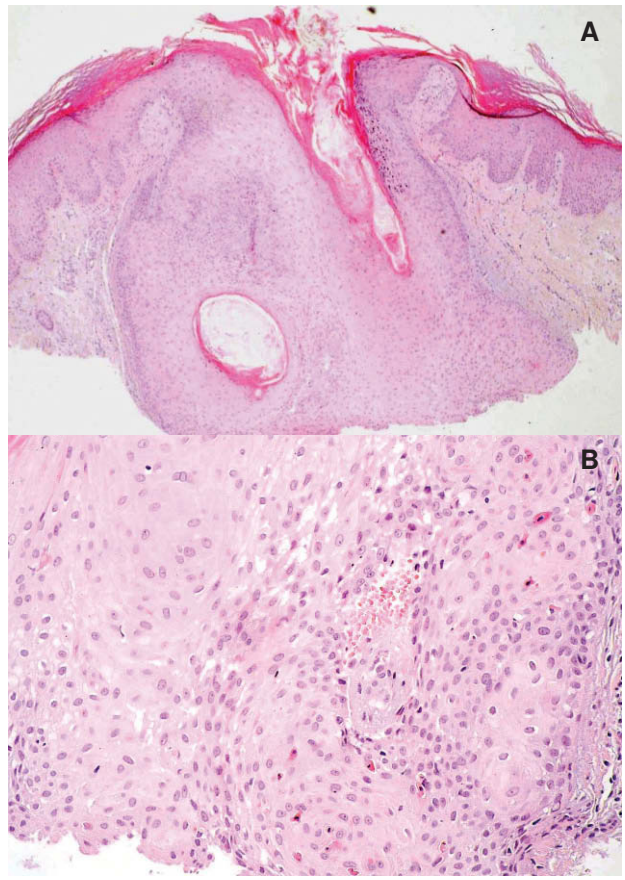

Figure 6A and B. Hyperkeratotic epithelium and acanthosis together with squamous whorls scattered through the squamous epithelium surrounding a hair follicle, with congested capillaries containing red blood cells. (A) Hematoxylin-eosin, ×100. (B) Hematoxylin-eosin, ×100.

Discussion

Cowden disease or multiple hamartoma syndrome is a rare genetic disorder characterized by the presence of multiple hamartomatous tumors of ectodermal, mesodermal, and endodermal origin. It was first described in 1963 by Lloyd and Dennis,[3] who named it in honor of the first patient in whom it was diagnosed; the patient presented multisystem disease with characteristic mucocutaneous lesions and abnormalities of the breast, thyroid, and gastrointestinal tract. In 1972, Weary et al[1] suggested that the term multiple hamartoma syndrome was more appropriate, as it better defines the association of these dysplasias in different organs.

The disease affects 1 of every 200 000 persons,[1] but this prevalence is probably an underestimate, as the clinical signs that these patients present are often very subtle and pass unnoticed by the doctor. It is inherited as an autosomal dominant trait with variable expression. The proportion of sporadic cases is uncertain (due to underdiagnosis of the disease), and it is assumed that 40% to 65% are familial (2 or more family members affected).[1] Its prevalence is somewhat higher in women and the majority of reported cases involve white patients.

Approximately 80% of patients with this disease present a germline mutation of the *PTEN* tumor suppressor gene located on chromosome 10q23.[5] Cowden disease has been included in the list of diseases associated with *PTEN*, which also includes Bannayan-Riley-Ruvalcaba syndrome,[6] Proteus and Proteus-like syndromes,[7] and Lhermitte-Duclos disease.[8] It is believed that the principal defect in Cowden disease is an abnormality in the regulation of cell proliferation. The protein product of the *PTEN* gene is a phosphatase that is involved in cell cycle regulation and apoptosis, and it acts as a tumor suppressor gene.[9,10] The tissues affected are those that have the capacity to proliferate, such as the epidermis, oral and gastrointestinal mucosas, and epithelia of the breast and thyroid. This mechanism would explain how *PTEN* mutations could in theory contribute to the development of hamartomas and sporadic

Table. Criteria That Must be Satisfied for the Operational Diagnosis

Operational diagnosis
Only cutaneous lesions if there are – At least 6 facial papules, of which 3 must be trichilemmomas, or – Facial cutaneous papules and oral mucosal papillomatosis, or – Oral mucosal papillomatosis and acral keratoses, or – At least 6 palmoplantar keratoses
Two major criteria, but 1 must be macrocephaly or Lhermitte-Duclos disease
One major criterion and 3 minor
Four minor criteria

benign and malignant tumors in patients with Cowden syndrome. Trichilemmomas in Cowden disease may be caused by mutations in *PTEN*, with a secondary overgrowth of the epithelium of the follicular infundibulum.

In the year 2000, the International Cowden Syndrome Consortium divided the clinical diagnostic criteria into pathognomic, major, and minor criteria.[11] The pathognomonic criteria include the facial trichilemmomas, mucosal lesions, acral keratoses, and papillomatous lesions. The major criteria include breast cancer, nonmedullary thyroid cancer, macrocephaly, Lhermitte-Duclos disease, and endometrial carcinoma; the minor criteria are other thyroid lesions, mental retardation, gastrointestinal hamartomas, fibrocystic disease of the breast, lipomas, fibromas, and genitourinary tumors or malformations. A series of criteria (Table) must be satisfied for the operational diagnosis of a patient. Our patient presented acral keratoses and mucosal lesions (pathognomic criteria), breast cancer, endometrial cancer, multinodular goiter, and macrocephaly (major criteria), and sphenoidal meningioma, inverted follicular keratosis, and verruca vulgaris (minor criteria).

Skin disease is present in more than 90% of patients and the characteristic mucocutaneous lesions usually start to appear during the second and third decades of life.[12,13] The presence of multiple facial trichilemmomas is diagnostic of Cowden disease,[11] but there is a series of alterations that, in their absence, must lead us to suspect this diagnosis (variants of infundibular follicular hyperplasia or tumors of the follicular infundibulum, keratosis, and lesions with an appearance similar to inverted follicular keratosis).[14,15] Lesions on other parts of the body can include seborrheic keratosis, verruca vulgaris or plana, lesions similar to acrokeratosis verruciformis, palmoplantar keratoderma, and lesions similar to trichilemmomas or inverted follicular keratosis.[16]

Regarding the neurological manifestations that usually accompany Cowden syndrome, the majority of cases published refer to Lhermitte-Duclos disease or dysplastic gangliocytoma of the cerebellum, though there are also several cases that associate meningioma with Cowden syndrome due to mutations in the *PTEN* gene.[4,17-19]

In contrast to the trichilemmomas, inverted follicular keratoses are not a pathognomic marker of Cowden disease, despite case reports in which the diagnosis of Cowden disease has been made in the absence of trichilemmomas and with the presence of inverted follicular keratosis, as in our case. Perhaps this aspect should be reappraised, as according to some authors, such as Ackerman and Requena, inverted follicular keratosis and trichilemmoma are basically the same lesion, that is, verruca vulgaris with trichilemmal differentiation. This possible viral origin was confirmed in 1991 by Hori, who used immunohistochemistry to demonstrate the presence of the common antigen of the human papilloma virus in an inverted follicular keratosis lesion. However, there are authors who favor other interpretations regarding the true nature of inverted follicular keratosis, including some who consider this lesion to be an irritated seborrheic keratosis, a tumor of the intraepidermal part of the follicular infundibulum, or an independent lesion.

Thus, although the majority of patients diagnosed with Cowden disease present facial trichilemmomas, the absence of these lesions in the presence of other lesions that show certain histological similarity, such as verruca vulgaris, inverted follicular keratosis, and trichilemmomas, must lead to a suspicion of Cowden disease.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Eng C. PTEN: One gene, many syndromes. Human Mutat. 2003;22:183-98.
2. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, et al. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet. 1997;16:64-7.
3. Lloyd K, Dennis M. Cowden's disease: A possible new symptom complex with multiple system involvement. Ann Intern Med. 1963;58:136-42.
4. Weary PE, Gorlin RJ, Gentry WC Jr, Comer JE, Greer KE. Multiple hamartoma syndrome (Cowden's disease). Arch Dermatol. 1972;106:682-90.
5. Nelen MR, Padberg GW, Peeters EA, Lin AY, van den Helm B, Frants RR, et al. Localization of the gene for Cowden disease to chromosome 10q22-23. Nat Genet. 1996;13:114-6.
6. Hendriks YM, Verhallen JT, van der Smagt JJ, Kant SG, Hilhorst Y, Hoefsloot L, et al. Bannayan-Riley-Ruvalcaba syndrome: further delineation of the phenotype and management of PTEN mutation-positive cases. Fam Cancer. 2003; 2:79-85.
7. Thiffault I, Schwartz CE, Der Kaloustian V, Foulkes WD. Mutation analysis of the tumor suppressor PTEN and the

glypican 3 (GPC3) gene in patients diagnosed with Proteus syndrome. Am J Med Genet A. 2004;130:123-7.
8. Abel TW, Baker SJ, Fraser MM, Tihan T, Nelson JS, Yachnis AT, et al. Lhermitte-Duclos disease: a report of 31 cases with immunohistochemical analysis of the PTEN/AKT/ mTOR pathway. J Neuropathol Exp Neurol. 2005;64:341-9.
9. Simpson L, Parson R. PTEN: Life as a tumor suppressor. Exp Cell Res. 2001;264:29-41.
10. Waite KA, Eng C. Protean PTEN: Form and function. Am J Hum Genet. 2002;70:829-44.
11. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet. 2000;37:828-30.
12. Starink TM, van der Veen JPW, Arwert F, de Waal LP, de Lange GG, Gille JJ, et al. The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet. 1986;29:222-33.
13. Longy M, Lacombe D. Cowden disease. Report of a family and review. Ann Genet. 1996;39:35-42.
14. Starink TM, Hausman R. The cutaneous pathology of facial lesions in Cowden's disease. J Cutan Pathol. 1984;11:331-7.
15. Starink TM. Cowden's disease: analysis of fourteen new cases. J Am Acad Dermatol. 1984;11:1127-41.
16. Starink TM, Hausman R. The cutaneous pathology of extrafacial lesions in Cowden's disease. J Cutan Pathol 1984;11:338-44.
17. Emmerson RW. Epidermodysplasia verruciformis and punctuate keratoderma. Brit J Dermatol. 1980;103:50-2.
18. Fritsch P, Pechlaner R, Czarnecki N, Hintner H. Das multiple hamartome syndrom (Cowden Syndrom). Hautarzt. 1981;32:285-91.
19. Lyons CJ, Wilson CB, Horton JC. Association between meningioma and Cowden's disease. Neurology. 1993;43: 1436-7.