

Erythrokeratoderma En cocardes with R32W Mutation in *GJB3*

Anna López-Ferrer¹, L Puig¹, M Nakamura³, MT Fernández-Figueras² and A Alomar¹

¹Dermatology Department. Hospital de la Santa Creu i Sant Pau. Barcelona, Spain

²Pathology Department. Hospital Germans Trias i Pujol. Badalona, Spain

³Department of Dermatology. University of Occupational and Environmental Health. Kitakyushu, Japan

Abstract

The term erythrokeratodermas is applied to a group of inherited disorders of keratinisation characterized by well demarcated erythematous lesions and hyperkeratotic plaques. Erythrokeratoderma *en cocardes* is an atypical variant characterised by the presence of transient hyperkeratotic and erythematous plaques. The pathogenetic mechanisms of most of the erythrokeratodermas are related to mutations in the connexin gene family, but until now, there is no information concerning the genetic alterations that are responsible for the appearance of the erythrokeratoderma *en cocardes*.

We report the case of a 31-year-old woman with a 5-year history of fixed erythematous plaques with scaly rims on the arms, trunk, axillae and limb flexures that disappeared spontaneously and recurred every summer. According to clinical features the diagnosis of erythrokeratoderma *en cocardes* was made. In this patient we have demonstrated the presence of a R32W mutation in the *GJB3* gene, but this might be a functionally inconsequential polymorphism.

Here in we report the first case of a patient with erythrokeratoderma *en cocardes* in whom a mutation in *GJB3* has been found, but the clinical implications of this finding remain to be elucidated.

Keywords: Connexins; Erythrokeratoderma *en cocardes*; Erythrokeratoderma variabilis; *GJB3*

Introduction

The term erythrokeratodemas is applied to a group of inherited disorders of keratinisation characterized by well demarcated erythematous lesions and hyperkeratotic plaques. Erythrokeratodermas have been divided into two major subtypes, erythrokeratoderma variabilis (EKV) (Mendes da Costa) [1] and progressive symmetric erythrokeratoderma (PSEK) (Gottron) [2, and several atypical variants [3]. EKV usually presents at birth or in early infancy and it is characterised by migratory irregularly shaped erythematous areas, that can be solid, annular or polycyclic, and vary in shape and position over hours or days, in association with hyperkeratotic, well-defined, more stable plaques, which may be associated with peeling or collarette-like scaling, and have a predilection for the extensor aspects of limbs, the lateral trunk and the buttocks, and tend to be symmetrical in distribution. Erythrokeratoderma *en cocardes* [4] and erythrokeratoderma with erythema gyratum repens-like lesions [5] are considered to be clinical variants of EKV, characterized by figurate, polycyclic and concentric (cockade-like) lesions that vary in shape in the course of hours or days and tend to recur in the course of several weeks, in association with hyperkeratotic, well-defined reddish plaques [3,6]. PSEK differs from EKV in the absence of migratory erythematous lesions and a greater incidence of palmoplantar keratoderma [3], and a frameshift mutation of the loricrin gene has been identified in a patient with a diagnosis of PSEK [7]. Nevertheless, there is an opinion that so-called PSEK with loricrin mutation probably corresponds to variant form of Vohwinkel syndrome, or loricrin keratoderma [3], and recent evidence suggests that the same *GJB4* mutation can cause either EKV [8] or a PSEK phenotype [9].

The pattern of inheritance of EKV is usually autosomal dominant, but cases consistent with autosomal recessive inheritance, as well as sporadic cases have been reported [10]. The major gene map locus for EKV is 1p34-1p35.1. Two disease related genes have been identified in the chromosomal region 1p34-35: *GJB3* and *GJB4*, which encode

for the gap junction proteins 3 and 4, also known as connexin 31 (Cx31) and connexin 30.3 (Cx30.3), respectively [11].

Connexins are gap junction proteins that mediate the exchange of metabolites, ions and second messengers between cells, and mutations of their genes have been associated with EKV (*GJB3*, *GJB4*), KID syndrome (*GJB2* encoding Cx26, and *GJB6*, encoding Cx30), palmoplantar keratoderma and Bart-Pumphrey syndrome (*GJB2*), and Clouston syndrome and pachyonychia congenita (*GJB6*) [12]; in addition, mutations in *GJB2* and less frequently *GJB6* are the main cause of nonsyndromic deafness worldwide [13]. Erythrokeratoderma with erythema gyratum repens-like lesions [5] has been described in a large kindred of Jewish and Kurdish origin; all affected members show fixed hyperkeratotic plaques, but in some members they coexist with variable erythematous plaques resembling erythema gyratum repens. A mutation in the Cx30.3 gene has been found in this family [14, and the corresponding phenotype, that has been reported in three other families and one sporadic case with standard EKV phenotypes [8], appears to be rather specific for this mutation [3].

As regards erythrokeratoderma *en cocardes* there are no data reported concerning the genes that are mutated, except for one case in which mutations of *GJB3* (or *GJB2*, encoding Cx26) were excluded. This patient was heterozygous for a non-disease associated polymorphism of *GJB4* [15].

***Corresponding author:** Anna López Ferrer, Dermatology Department, Hospital de la Santa Creu i San Pau, C/ Sant Antoni Maria Claret 167, 08025 Barcelona, Spain, Tel: 34935537007; Fax: 34935537008; E-mail: alopezfe@santpau.cat

Received September 23, 2010; **Accepted** December 28, 2010; **Published** December 29, 2010

Citation: López-Ferrer A, Puig L, Nakamura M, Fernández-Figueras MT, Alomar A (2010) Erythrokeratoderma En cocardes with R32W Mutation in *GJB3*. J Clin Exp Dermatol Res 1:113. doi:10.4172/2155-9554.1000113

Copyright: © 2010 López-Ferrer A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



Herein we report the case of a patient with erythrokeratoderma *en cocardes* with no family history of the disease in whom a mutation in the *GJB3* gene (R32W) was demonstrated.

Case Report

A 31-year-old woman presented to our Dermatology Department with a 5-year history of erythematous plaques with scaly rims on the arms, trunk and flexures, that were fixed, with minimal variation for several months and disappeared spontaneously, recurring every summer. She had no associated diseases, including atopic dermatitis, and did not take any medication. She had no affected family members and there was no history of familial consanguinity.

Physical examination showed large erythematous and mildly hyperkeratotic patches, with figurate and occasionally cockade-like ('cocarde') areas resembling erythema annulare centrifugum. The patches had geographical circinate borders with an erythematous rim peripheral to a fine collarette of desquamation (Figure 1). They were symmetrically distributed on the upper trunk, upper arms, thighs and buttocks (Figure 2). There were no alterations on her palms



Figure 1: Hyperkeratotic plaques in axilla surrounded by erythematous rims.



Figure 2: Hyperkeratotic plaques with collarette-like scaling in buttocks.

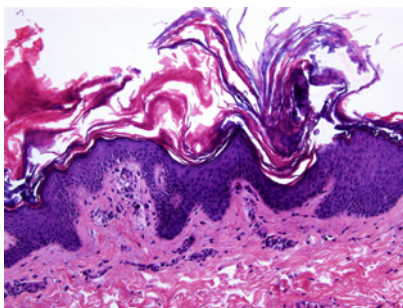


Figure 3: Histological examination of the skin showed acanthosis with slight papillomatosis and orthokeratotic hyperkeratosis with a mild perivascular lymphocytic infiltrate on the upper dermis.

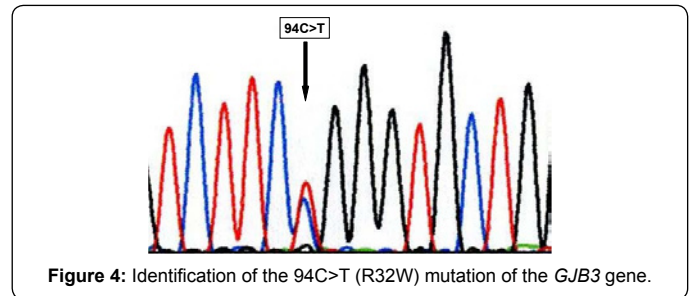


Figure 4: Identification of the 94C>T (R32W) mutation of the *GJB3* gene.

and soles, and her hair, teeth, and nails were also normal. General physical examination showed no enlarged lymph nodes, neurologic or eye abnormalities. Audiometric analysis revealed no hearing alterations in the patient.

Results of KOH preparations and mycologic and bacterial cultures of skin scrapings were repeatedly negative.

Laboratory analysis results were normal, including blood cell counts, liver and kidney function tests and antinuclear antibody, anti-Ro and anti-La determinations. Histopathologic study of a cutaneous punch biopsy showed irregular acanthosis with slight papillomatosis and orthokeratotic hyperkeratosis with preservation of a normal granular layer. No dyskeratotic cells were observed. On the upper dermis there was a mild perivascular lymphocytic infiltrate (Figure 3). These findings were non-specific but consistent with the diagnosis of erythrokeratoderma.

The topical administration of tacrolimus 0.1%, calcipotriol and adapalene was partially efficacious for the eruption. During follow-up the patient presented several periods of remission followed by periods with affected skin.

To study connexin gene mutations, genome DNA was extracted from peripheral blood samples [10]. PCR amplification and direct sequencing of the *GJB3* and *GJB4* genes revealed a missense mutation c.94C>T (R32W) in the *GJB3* gene encoding Cx31 (Figure 4), whereas no alterations in the *GJB4* gene were detected.

Discussion

Erythrokeratodermas are a group of genodermatoses that share clinical features but are heterogeneous at the genetic level [16]. The diagnosis of erythrokeratodermas is usually made according to typical clinical features. In our case, the patient presented with symmetrical erythematous, mildly desquamative patches with geographic configuration and circinate borders with peripheral collarette and occasional concentric and rosette-like appearance. The lesions tended to be fixed for 5-6 months and disappeared spontaneously, reappearing again after several months of remission, and there was no palmoplantar involvement. Tinea corporis, ichthyosis linearis circumflexa, subacute lupus erythematosus, erythema gyratum repens and other conditions included in the differential diagnosis of EKV were ruled out. According to clinical criteria and histopathologic correlation, the diagnosis of (sporadic) erythrokeratoderma *en cocardes* was established in this patient.

EKV is usually characterized by fixed hyperkeratotic plaques, but several authors have described periods of remission in certain patients [16], that suggest the diagnosis of the subtype erythrokeratoderma *en cocardes*.

In our case, the patient was asymptomatic during childhood and the first signs of disease appeared in adulthood. This is not



consistent with the typical cases of EKV described in the literature, because clinical lesions usually appear during the first year of life [3,16]. Nevertheless, EKV lesions can seldom be observed for the first time in teenagers [6] and adult patients [17].

One of the typical signs referred by our patient was the aggravation of the lesions in summer. This is consistent with previous cases reported in the literature corresponding to erythrokeratoderma *en cocardes* [6,18], whereas the cases with classical EKV present aggravation in winter [19].

As regards genetic studies, several mutations of *GJB3* and *GJB4* (coding for connexin 31 and connexin 30.3, respectively) have been reported in both familial and sporadic cases of EKV [8,9,11,19,20], suggesting a genetic heterogeneity in EKV. Lesions in patients with EKV due to Cx30.3 tend to be more annular in appearance [8,14] than EKV of the Mendes da Costa type (Cx31) [11]. In the family with erythrokeratoderma with erythema gyratum repens-like lesions reported by Landau et al. [5] a mutation in the *GJB4* gene have been reported [11], and other families with *GJB4* mutations also show marked annular lesions [5]. Interestingly enough, all the four Japanese patients with EKV reviewed by Nakamura et al. [10] were female and without family history, as in our case and no mutations in *GJB3* and *GJB4* could be demonstrated in them.

In a Japanese girl with erythrokeratoderma *en cocardes* no mutations of *GJB3* (or *GJB2*, encoding Cx26) were detected, and the patient was found to be heterozygous for a non-disease associated polymorphism of *GJB4* [15].

In our patient we found a missense mutation 94C>T (R32W) in the *GJB3* gene that has been previously found in patients with palmoplantar keratoderma and profound deafness [21]. The arginine residue is present in the first transmembrane domain of the protein and is conserved in all connexin species. In palmoplantar keratoderma with deafness, the R32W mutation in the *GJB3* gene is associated with mutations in the *GJB2* gene, correlating with the severity of hearing impairment [21]. Nevertheless, according to López-Bigas et al. [22], R32W is a rather common polymorphism (7.5%) in the Spanish population, having been detected in 17% of control subjects in the population they analysed.

Further studies are required to clarify the genetic and phenotypic variability of the erythrokeratodermas. The R32W mutation of *GJB3* might be related to the erythrokeratoderma *en cocardes* subtype, but this missense mutation has been considered to be a functionally inconsequential polymorphism [23,24], and other as yet unidentified (connexin?) genes might be etiologically involved in EKV, as previously suggested [10].

References

- Mendes da Costa (1925) Erythro- et keratoderma variabilis in a mother and a daughter. Acta Derm Venereol 6: 255-261.
- Gottron HA (1923) Congenital symmetrical progressive erythrokeratoderma. Arch Dermatol Syph 7: 416.
- Rogers M (2005) Erythrokeratodermas: A classification in a state of flux? Australas J Dermatol 46: 127-145.
- Degos R, Delzant O, Morival H (1947) Erythème desquamatif en plaques, congénital et familial (génodermatose nouvelle?). Bull Soc Fr Derm Syph 54 : 442.
- Landau M, Cohen-Bar-Dayan M, Hohl D, Ophir J, Wolf CR, et al. (2002) Erythrokeratoderma variabilis with erythema gyratum repens-like lesions. Pediatr Dermatol 19: 285-292.
- Rajagopalan B, Pulimood S, George S, Jacob M (1999) Erythrokeratoderma en cocardes. Clin Exp Dermatol 24: 173-174.
- Ishida-Yamamoto A, McGrath JA, Lam H, Iuzuka H, Friedman RA, et al. (1997) The molecular pathology of progressive symmetric erythrokeratoderma: a frameshift mutation in the loricrin gene and perturbations in the cornified cell envelope. Am J Hum Genet 61: 581-589.
- Richard G, Brown N, Rouan F, Van der Schroeff JG, Bijlsma E, et al. (2003) Genetic heterogeneity in erythrokeratoderma variabilis: novel mutations in the connexin gene GJB4 (Cx30.3) and genotype-phenotype correlations. J Invest Dermatol 120: 601-609.
- van Steensel MA, Oranje AP, van der Schroeff JG, Wagner A, van Geel M (2009). The missense mutation G12D in connexin 30.3 can cause both erythrokeratoderma variabilis of Mendes da Costa and progressive symmetric erythrokeratoderma of Gottron. Am J Med Genet A 149: 657-661.
- Nakamura M, Ishikawa O (2007) Erythrokeratoderma variabilis without GJB3 and GJB4 mutation: a review of Japanese patients. Br J Dermatol 157: 410-411.
- Plantard L, Huber M, Macari F, Meda P, Hohl D (2003) Molecular interaction of connexin 30.3 and connexin 31 suggests a dominant-negative mechanism associated with erythrokeratoderma variabilis. Hum Mol Genet 12: 3287-3294.
- Richard G (2003) Connexin gene pathology. Clin Exp Dermatol 28: 397-409.
- Rabionet R, Gasparini P, Estivill X (2000) Molecular genetics of hearing impairment due to mutations in gap junction genes encoding beta connexins. Hum Mutat 16: 190-202.
- Macari F, Landau M, Cousin P, Mevorah B, Brenner S, et al. (2000) Mutation in the gene for connexin 30.3 in a family with erythrokeratoderma variabilis. Am J Hum Genet 67: 1296-1301.
- Ishida-Yamamoto A, Kelsell D, Common J, Houseman MJ, Hashimoto M, et al. (2000) A case of erythrokeratoderma variabilis without mutations in connexin 31. Br J Dermatol 143: 1283-1287.
- Hendrix JD, Greer KE (1995) Erythrokeratoderma variabilis present at birth: case report and review of the literature. Pediatr Dermatol 12: 351-354.
- Cram DL (1970) Erythrokeratoderma variabilis and variable circinate erythrokeratodermas. Arch Dermatol 101: 68-73.
- Hacham-Zadeh S, Even-Paz Z (1978) Erythrokeratoderma variabilis in a Jewish Kurdish family. Clin Genet 13: 404-408.
- Feldmeyer L, Plantard L, Mevorah B, Huber M, Hohl D (2005) Novel mutation of connexin 31 causing erythrokeratoderma variabilis. Br J Dermatol 152: 1062-1094.
- Renner R, Paasch U, Slmon JC, Froster UG, Heinritz W (2008) A new mutation in the GJB3 gene in a patient with erythrokeratoderma variabilis. J Eur Acad Dermatol Venereol 22: 750-751.
- Kelsell DP, Wilgoss AL, Richard G, Stevens HP, Munro CS, et al. (2000) Connexin mutations associated with palmoplantar keratoderma and profound deafness in a single family. Eur J Hum Genet 8: 469-472.
- López-Bigas N, Rabionet R, Arbones ML, Estivill X (2001) R32W variant in Connexin 31: mutation or polymorphism for deafness and skin disease? Eur J Hum Genet 9: 70.
- Mhatre AN, Weld E, Lalwani AK (2003) Mutation analysis of connexin 31 (GJB3) in sporadic non-syndromic hearing impairment. Clin Genet 63: 154-159.
- Rouan F, Lo CW, Fertala A, Wahl M, Jost M, et al. (2003) Divergent effects of two sequence variants of GJB3 (G12D and R32W) on the function of connexin 31 *in vitro*. Exp Dermatol 12: 191-197.

