

Epidermal nevi: a retrospective study of 133 cases

Gimena Castro Pérez,* Patricia Della Giovanna,** Hugo Néstor Cabrera,*** Sandra García****

ABSTRACT

Epidermal nevi are common skin dysembryoplasias that may be present at birth or develop during early childhood. Clinically they are hyperkeratotic, verrucous lesions, which, if associated with skeletal, neurological and ocular abnormalities conform an epidermal nevus syndrome. We present 133 cases among which the most frequent clinical presentation was nevus simplex followed by ILVEN. The predominant histological feature was the classic pattern, followed by the epidermolytic hyperkeratosis pattern. The prevalence of the epidermal nevus syndrome was 2.21%. (Dermatol. Argent. 2011; 17(1):40-46).

Key words

epidermal nevus, verrucous nevus, epidermal nevus syndrome

Submission date: 2/8/2010 | **Approval date:** 12/8/2010

Introduction

Epidermal nevi are circumscribed skin malformations with a predominant epidermal component. Clinically they tend to manifest as hyperkeratotic, verrucous, pigmented, rough plaques with varied histological patterns. They may appear in isolation or they may conform a syndrome, as in the case of the epidermal nevus¹.

We have carried out a retrospective study of all the patients with clinical and/or histological diagnosis of epidermal nevus evaluated at the Dermatology Department at Prof Dr Alejandro Posadas National Hospital between January 1979 and September 2009.

* Chief of Residents

** Dermatology Department Chief

*** Consultant Professor

**** Chief of Dermopathology Section at the Pathological Anatomy Department

Dermatology Department at Prof Dr Alejandro Posadas National Hospitalization

Contact: Dr Gimena Castro Pérez, Martín Rodríguez 3789, Carapachay (1606), Vicente López, BA, Argentina

Objectives

- To gather information about all the cases of epidermal nevi evaluated at our Department during the mentioned period.
- To define its main clinical and histopathological features.
- To evaluate the presence of associations with other cutaneous lesions and neoplasias.
- To determine the prevalence of the epidermal nevus syndrome in our population.

Material and methods

We have used: the picture archive of the Dermatology Department, the database of the Pathological Anatomy Department and medical histories of patients selected from the Archive at the Prof Dr Alejandro Posadas National Hospital.

We gathered information about 133 patients in total and described the following items: consultation age, sex, clinical variety of epidermal nevus, location, histopathological features, associations and possible inclusion within the the epidermal nevus syndrome.

Results

Regarding the age of the patients when they first consulted: 87 (65.41%) were evaluated before 20 years of age (Graph 1); consultation was more frequently made by females (55.64% of the cases) (Graph 2).

According to the classification posited by Cabrera and García¹, seven clinical categories of epidermal nevi were taken into account and it was observed that more than half the cases corresponded to simple or vulgar epidermal nevus: 70 cases (52.63%) (Graph 3).

With reference to the location of the nevi, it was found that:

- Among the simple epidermal nevi (70 cases), the most affected area was the thorax (21 cases, 30%) followed by head and neck (15 cases, 21.4%) (Graph 4).
- Out of the 18 systematized epidermal nevi studied, 14 cases (77.8%) were located on the thorax while the remaining 4 cases (22.2%) corresponded to neves unius lateris located unilaterally (3 on right hemibody and 1 on left hemibody).
- Out of the neviform keratosis of the nipple and areola (NKN) (8 cases): 7 cases were type I and affected only the nipple (87.5%). We had 1 type II case which affected the nipple and areola (12.5%).
- The ILVEN were most frequently distributed on limbs (19/29) (Graph 5).

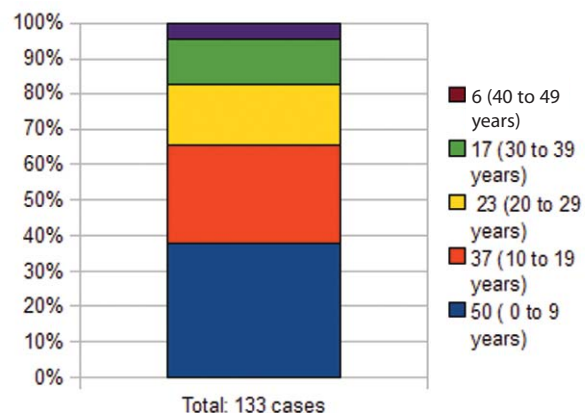
Histopathological study

- A biopsy was done in 80 cases: 29 ILVEN, 8 neviform keratosis of the nipple and 43 clinically classic and/or particularly looking epidermal nevi.
- The serial histopathological study of 43 epidermal nevi samples (excluding ILVEN and NKN) yielded that, out of the three characteristic patterns of epidermal nevi described in the literature, the most frequent were hyperkeratosis, acanthosis and papillomatosis (35 samples, 81.4%), followed by epidermolytic hyperkeratosis (6 cases, 13.9%) and acantholytic dyskeratosis (2 cases, 4.7%).
- There were no atypical findings in the histological studies of the ILVEN or neviform keratoses of the nipple.

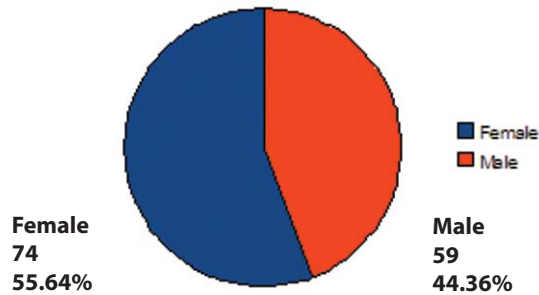
Associations

- We observed that 10 patients (7.5% of the total studied) presented associations not included within the epidermal nevus syndrome, such as other nevi and ulcerated hemangioma in one case. The most frequent associated nevus was nevus of Jadassohn followed by nevus pigmentosus and hypoplastic nevus pilosus.
- We had a nevus unius lateris case associated to prolactin macroadenoma (not included in non-syndromic associations).
- In our study, we have not found any patients with neoplasia associated to or derived from the epidermal nevus.
- The review of our patients yields 3 cases of epidermal nevus syndrome out of a total of 133 cases (2.21%).

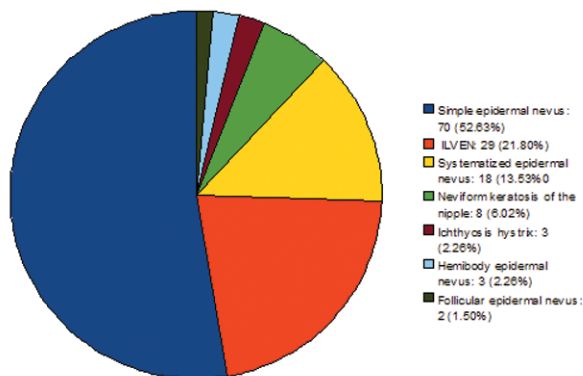
GRAPH 1: Distribution according to first consultation age



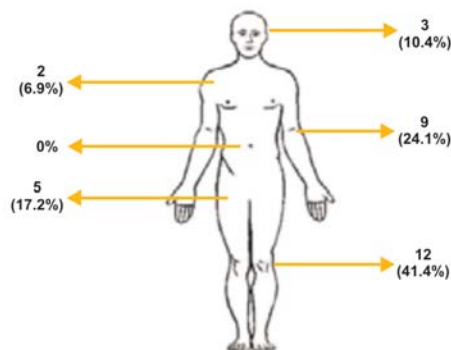
GRAPH 2: Distribution by sex. 133 cases



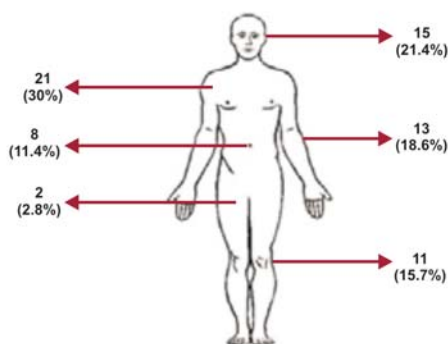
GRAPH 3: Distribution by clinical category



GRAPH 4: Distribution of simple epidermal nevi



GRAPH 5: Distribution of ILVEN



Comments

Epidermal nevi are lesions of malformative origin which appear at birth or at an early age with a prevalence of 1 every 1,000 neonates. Traditionally they have been classified according to their clinical characteristics as, in spite of the fact that a genetic origin is suspected, its etiopathogenesis remains unknown. They have also been grouped into organoid -nevi with different histogenetic structures- and non-organoid.

Nowadays, we may speak of a histo-genetic classification of epidermal nevi based on their traditional histopathological characteristics and the results of genetic studies described in the world literature in the past decade^{2,3}.

Epidermal nevi tend to manifest as linear lesions, single or multiple, circumscribed or systematized, which follow Blaschko's lines. This clinical characteristic suggests that genetic mosaicism could be responsible for epidermal nevi.

From the histological point of view, non-organoid epidermal nevi are divided into those which evidence epidermolytic hyperkeratosis and non-epidermolytic ones.

During the study of a family who suffered from epidermolytic hyperkeratosis, a disease caused by the mutations of cytokeratins 1 and 10 genes, Paller *et al.*² observed that some members of the same family who did not show any clinical manifestations of the disease had extense epidermal nevi. These nevi histologically evidenced epidermolytic hyperkeratosis and the above mentioned mutations on the lesion. However, such findings could not be detected on healthy skin around the lesion. This would confirm that epidermal nevi with epidermolytic hyperkeratosis would be the expression of genetic mosaicism caused by postzygotic mutations of cytokeratins 1 and 10 genes in cells intended to become keratinocytes. In turn, Hafner *et al.*³ studied 33 patients with non-organoid, non-epidermolytic epidermal nevi (NONEEN) who evidenced genetic mosaicism caused by cell lines with mutations of fibroblast growth factor receptor gene type 3 (FGFR3). They found that the most frequent mutation in these nevi was R248C and they described the existence of dozens of different mutations within the same gene capable of yielding equal clinical manifestations. These changes would not manifest on the healthy skin of the patients studied, which proves that mosaicism is responsible for their emergence.

The FGF receptor family (FGFR) consists of four tyrosine-kinase transmembrane receptors (FGFR 1-4) related to angiogenesis, embryogenesis and tissue homeostasis processes. FGFR3 gene mutations give rise to two of their isoforms: isoform FGFR3 IIIb, which expresses itself in epithelial cells, and FGFR3 IIIc, which expresses itself in mesenchymal cells. As they interact with their specific

ligands, the FGFR3 phosphorylation generates different intracellular signaling pathways responsible for the expression of proteins linked to severe dominant autosomal skeletal disorders such as achondrodysplasia and thanatophoric dysplasia, certain neoplasias (low grade urinary tract adenocarcinoma) and cutaneous malformations such as NONEEN³⁻⁵.

Therefore, from the histogenetic point of view, there are two large groups of non-organoid epidermal nevi: the ones that evidence epidermolytic hyperkeratosis (Photo 1) and are related to mutations in cytokeratins 1 and 10 genes (13.9% of biopsies in this study); and the non-epidermolytic ones (NONEEN), related to the FGFR3 gene mutations (86.1% of biopsies in this study) (Photo 2). The latter group is characterized by the possible associations with musculoskeletal and neoplastic pathologies⁴.

Our study included 70 patients with simple epidermal nevi which were most frequently distributed on thorax (30%), followed by head and neck (15 cases, 21.4%), upper limb (18.6%), lower limb (15.7%), abdomen (11.4%) and genitalia (2.8%) (Photo 3). From the clinical point of view, we have noted the presence of a porokeratotic simple epidermal nevus and a hypopigmented one (Photo 4). We have not found any syndromic associations in any of them even if they have occasionally been described as constituents of syndromic complexes different from the epidermal nevus syndrome. Such is the case of the CHILD syndrome, in which there is another variant of epidermal nevus caused by mutations in NSDHL protein encoding genes located in the Xq28 chromosome³.

Systematized epidermal nevi are defined as those nevi which are located on a certain body segment and usually follow a dermatome, a metamer, Blaschko's lines or segmentation lines^{1,5}. Within this group, the cases which evidence epidermolytic hyperkeratosis are more frequent⁶⁻⁹.

This category includes nevus unius lateris, which is considered a paraneoplastic lesion by some authors owing to the fact that some cases have been published in which breast and esophagus cancer were associated⁵. In our experience, this was a fortuitous event and we believe it is more appropriate to consider nevus unius lateris as a systematized epidermal nevus variant which may occasionally behave as a marker of internal pathology, given that none of the four cases we observed presented associated malignant neoplasia and only one had an accompanying benign tumor (prolactin macroadenoma).

Neviform keratosis of the areola, nipple or both is an infrequent pathology predominant in females and, according to Lèvy and Franckel's classification, 3 types may be observed: type I, by extension of a nearby verrucous nevus (Photo 5); type II, as part of a generalized dermatosis; and lastly type III, idiopathic or nevoid^{9,10}.

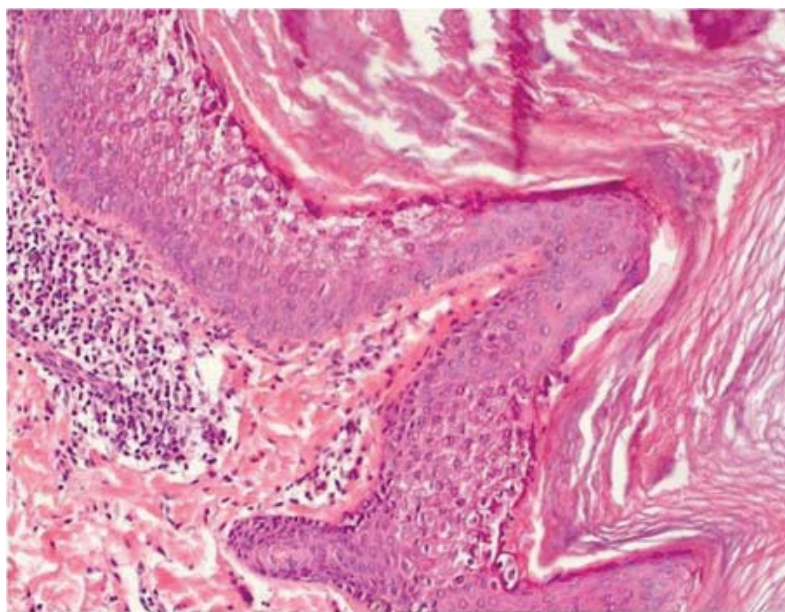


Photo 1: Epidermal nevus with epidermolytic hyperkeratosis (H & E).

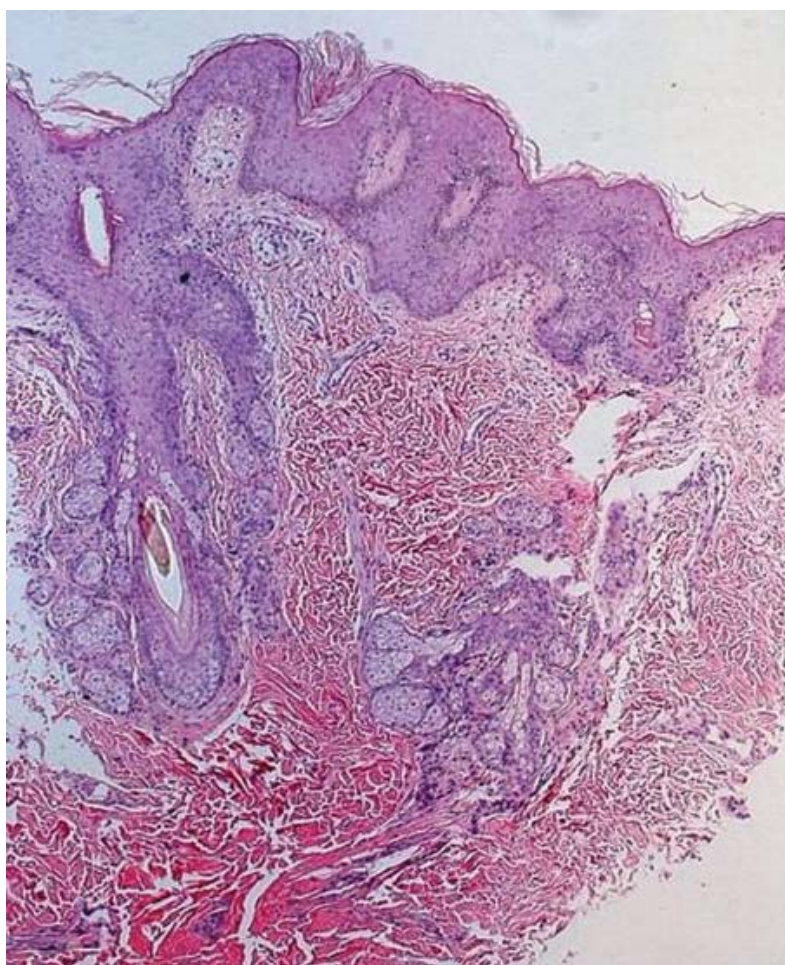


Photo 2: NONEEN (H & E).

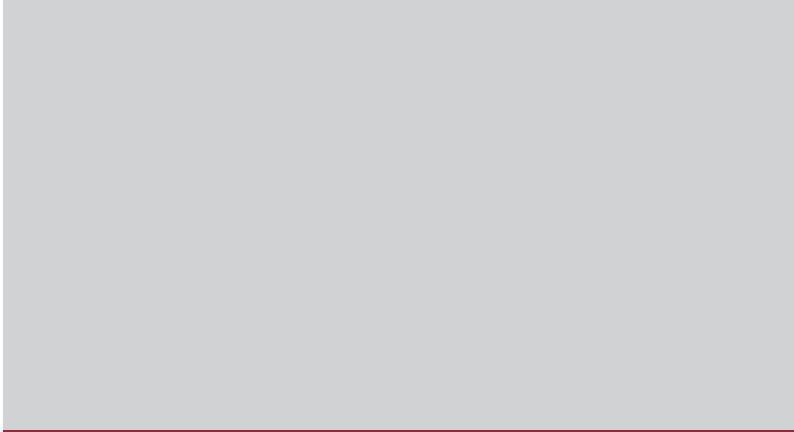


Photo 3: Simple epidermal nevus.



Photo 4: Porokeratotic epidermal nevus.

7 of the patient in our study correspond to the latter category, and in coincidence with the literature, they were all women with bilateral, asymptomatic, chronic lesions without associations to neoplastic or endocrinological pathology. Only one case was within type I, by extension of a nearby verrucous nevus^{9,10}.

Regarding the location of ILVEN, we have found a higher rate of genitalia involvement than has been reported in the literature (5 cases, 17.2% of ILVEN in our study), and no abdomen involvement (Photo 6). All ILVEN cases included in this paper were confirmed by histopathological study which evidenced the present of acanthosis, hypogranulosis and the characteristic alternation between parakeratosis and orthokeratosis. We have also observed cases with psoriasiform or spongiotic patterns.

Lever¹⁶ defined ichthyosis hystrix as a bilateral linear epidermal nevus which involves over 50% of the body surface and Perez O. G. et al posit that this type of nevus can range from mild, moderate or severe according to the extension and thickness of hyperkeratosis and its diagnosis may be made without the presence of cutaneous horns or thorns⁶. We were able to study three patients with these clinical features and we observed that they did not present any histopathological differences with NONEEN, i.e. we did not find epidermolytic hyperkeratosis or acantholytic dyskeratosis or recognize any associations with other pathologies.

The epidermal nevus syndrome was first described by Tobias in 1927. However, it was Solomon¹⁵ who coined the term "epidermal nevus syndrome" to refer to the set of cutaneous and extracutaneous alterations associated to these nevi. This is an entity which responds to the acronym CSNO due to the presence of Cutaneous, Skeletal, Neurological and Ocular alterations. Our paper demonstrated a syndrome prevalence of 2.21% in the studied population (133 patients). In all the cases the epidermal nevus was linear, not epidermolytic, as is described in the literature^{1,2,17-19}. As far as extracutaneous manifestations are concerned, it was observed that all the patients presented neurological alterations (convulsions and mental retardation) and skeletal alterations (kyphoscoliosis, syndactyly, bone cysts); only one had ocular alterations and none had associated vascular pathology or cancer. Finally, we noted the presence of other non-syndromic associations of the epidermal nevi studied: mainly other nevi, among which the nevus of Jadassohn occurred most frequently (and for some authors, the organoid variant of the epidermal nevus), followed by the nevus pigmentosus, hypoplastic nevus pilosus and a case of ulcerated hemangioma¹⁹ (Photos 7 and 8).

Conclusions

We evaluated 133 patients with epidermal nevi during a period of 30 years, which constitutes the largest set of cases under study in the literature consulted.

We found demographic data which coincide with national and international literature in that the majority of patients consulted at an early age (65.41% before 20 years) and they were mostly female (55.64%).

The most frequent clinical presentation was NONEEN - and within this group, simple epidermal nevi- followed by ILVEN.

Among the systematized epidermal nevi we found a high occurrence of unius lateris and the histological study of one of these patients evidenced epidermolytic hyperkeratosis in association with prolactin macroadenoma. We have not found any cases of nevus unius lateris associated to cancer.

Out of the 8 cases of neviform keratosis of the nipple and areola, 7 (87.5%) corresponded to the idiopathic variant and only the nipple was affected, and only one case (12.5%) was within type I by extension of a verrucous nevus. We did not find any cases associated with other dermatoses, endocrinological disorders or affecting males. The ILVEN had a greater representation than in the literature (21.8% vs 10.1% respectively) and occurred predominantly in females (2.2:1) and mostly affected genitalia¹⁰.

We observed three cases of ichthyosis hystrix and their biopsies did not evidence epidermolytic hyperkeratosis or other associated pathologies.

A cutaneous biopsy was done in 80 cases and in the 43 epidermal nevi (no ILVEN, no NKN) we observed the three histological patterns described in the literature with the following frequency: classic pattern, 81.4%; epidermolytic hyperkeratosis, 13.9%; acantholytic dyskeratosis, 4.7%. We determined that 86.1% of them corresponded to NONEEN and the rest to the epidermolytic hyperkeratosis group. This allowed us to determine their possible origin, explain their clinical-pathological characteristics, understand some of the associations typical of the epidermal nevus syndrome and establish a relationship with neoplasias not considered so far^{3,4}.

We did biopsies of all the ILVEN and NKN but we did not obtain any atypical findings in their histological studies.

As far as non-syndromic associations are concerned, we observed they were predominantly other nevi, the most frequent of which was Jadassohn's.



Photo 5: Type I neviform keratosis of the nipple and areola.



Photo 6: ILVEN (Inflammatory Linear Verrucous Epidermal Nevus).

We noted the absence of neoplastic transformations of the studied nevi or their association with malignant pathology.

The epidermal nevus syndrome in our study demonstrated a prevalence of 2.21% (3 patients) and it was associated to extensive linear forms in all cases, so we emphasize the importance of ruling out associated pathology in every extensive linear epidermal nevus. Neurological and musculoskeletal alterations were observed in absolutely all the patients with this entity.

Bibliography

1. Cabrera H.N. y García S.M. Nevos epidérmicos, Editorial Actualizaciones Médicas, Buenos Aires, 1998.
2. Paller A.S., Syder B.A., Chan Y.M., Yu Q.C. et ál. Genetic and clinical mosaicism in a type of epidermal nevus, *N. Engl. J. Med.*, 1994,331:1408-415.
3. Hafner C., Van Oers J., Vogt T., Landthaler M. et ál. Mosaicism of activating FGFR3 mutations in human skin causes epidermal nevi, *J. Clin. Invest.*, 2006, 116:2201-2207.
4. Hernández M., Toll A., Baselga E., Ribé A. et ál. Fibroblast growth factor receptor 3 mutations in epidermal nevi and associated low grade bladder tumors. *J. Invest. Dermatol.*, 2007, 127:1664-1666.
5. Hafner C., Klein A., Landthaler M. y Vogt T. Clonality of basal cell carcinoma arising in an epidermal nevus. New insights provided by molecular analysis, *Dermatology*, 2009, 218:278-281.
6. Pérez O.G., Casas J., Grosso J.C., Lubrano C. et ál. Nevo epidérmico sistematizado. *Dermatol. Argent.*, 2004, 3:194-198.
7. Boente M.C., Frontini M.V., Asial R.A. y Acosta M.I. Nevo epidérmico con hiperqueratosis epidermolítica. *Rev. Arg. Derm.*, 1994, 75:15-17.
8. Soler C.I., Cabrera H.N., Gómez M.L., Hiperqueratosis neviforme de pezón y aréola mamaria: revisión de la literatura a propósito de dos casos de queratosis neviforme de pezón, *Arch. Argent. Dermat.*, T. 1985, 35: 269-274.
9. Kaplan H., Lacentre E., Grosman M. Queratosis neviforme de pezón y aréola mamaria, *Arch. Argent. Dermat.*, 1984, 34: 223-227.
10. Gatti J.C., Cabrera H.N., Cardama J.E., Gabrieli M. et ál. Nevos epidérmicos y nevos dermatíticos (NEVIL), *Rev. Argen. Dermatol.*, 1978, 59:205-208.
11. González M.E., Consigli J.E., Giovo M.E., Chiapuis J.M. et ál. Nevo epidérmico verrugoso inflamatorio lineal, *Dermatol. Argent.*, 1999, 5:151-154.
12. Carbó Amoroso E., Díaz M.G., Guardati M.V., Reyes M.A. et ál. Nevo epidérmico inflamatorio lineal (NEVIL): presentación en edad adulta, *Rev. Argent. Dermatol.*, 2008, 89:90-95.
13. Valdez R.P., Baliña L.M., Kien M.C. Nevo epidérmico verrugoso inflamatorio (NEVIL) de disposición bilateral, *Rev. Argent. Dermatol.*, 1983, 64:276-280.
14. Cosentino N.R., Cabrera H.N., Gómez M.L. y Boffi A. Neviles tardíos, *Rev. Argent. Dermatol.*, 1984, 65:95-100.
15. Solomon L.M., Fretzin D.F., Dewald R.L. The epidermal nevus syndrome, *Arch. Dermatol.*, 1968, Mar, 97:273-285.
16. Lever W.F. *Histopathology of the skin*, 4° edición. Filadelfia. J.B. Lippincott; 1976, 485.
17. Pierini D.O. Nevos con manifestaciones extracutáneas, *Arch. Argent. Dermatol.*, 1975; 25:103-112.
18. Goldberg L.H., Scott A.B., Collins S.A., Siegel D.M. The epidermal nevus syndrome: case report and review, *Pediatr. Dermatol.*, 1987; 4:27-33.
19. Cabrera H.N., Pietropaolo N., y Mazzini R. Nevo epidérmico sistematizado cutáneo mucoso con nevo lanudo, nevo sebáceo y nevo pigmentario plano, *Arch. Argent. Dermat.*, 1986; 36:115-122.

Photo 7: Nevus of Jadassohn.

Photo 8: Hypoplastic nevus pilosus accompanying epidermal nevus.