therapy, local tacalcitol or Acitretinoin for disseminated variants.[2,3]

No data have been reported so far about the link between porokeratosis and exemestane or trastuzumab. As the patient is still receiving the same oncological treatment, persistence of the lesions could be linked with either the immunotherapy or the antihormonal therapy. Porokeratosis is a disorder of keratinization and antibodies targeting the HER-family receptors can cause disorders at this level The possibility that eruptive porokeratosis must be considered as a paraneoplastic phenomenon in our case cannot be completely ruled out. Nevertheless, the long period of time between both conditions, the fact that skin eruption persists although tumor response to the treatment and a time association with the treatment starting supports a drug induced phenomenon in our opinion.

Références

1. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. J Am Acad Dermatol. 2015;72:221–36.
2. Brauer JA, Mandal R, Walters R, Solomon G, Kundu RV, Strober BE. Disseminated superficial porokeratosis. Dermatol Online J. 2010 15;16:20.
3. Shoimer I, Robertson LH, Storwick G, Haber RM. Eruptive disseminated porokeratosis: A new classification system. J Am Acad Dermatol. 2014;71:398–400.
4. Jung JY, Yeon JH, Ryu HS, Youn SW, Park KC, Huh CH. Disseminated superficial porokeratosis developed by immunosuppression due to rheumatoid arthritis treatment. J Dermatol. 2009;36:466–7.
5. Buhl T, Wienrich BG, Sieblist C, Schön MP, Seitz CS. Development of segmental superficial actinic porokeratosis during immunosuppressive therapy for pemphigus vulgaris. Acta Derm Venereol. 2010;90:212-3.
6. Goulding JM, Teoh JK, Carr RA, Humphreys F, Gee BC. Eruptive disseminated superficial porokeratosis with rapid resolution: A drug-induced phenomenon? Clin Exp Dermatol. 2009;34:875-95.
7. Torres T, Velho GC, Selores M. Disseminated superficial porokeratosis in a patient with cholangiocarcinoma: A paraneoplastic manifestation? An Bras Dermatol. 2010;85:229–31.

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Expanding the genetic profile of Hay-Wells syndrome☆

Ampliando el perfil genético del síndrome de Hay-Wells

To the Editor:

Hay-Wells syndrome, also known as AEC syndrome (ankyloblepharon-ectodermal dysplasia-clefting syndrome, Online Mendelian Inheritance in Man [OMIM] 106260) is a rare, autosomal dominant genetic disorder, associated with a heterozygous mutation in the TP63 gene. AEC syndrome is defined by ectodermal abnormalities of the skin, teeth, hair, and nails, in combination with characteristic eyelid fusion and facial clefting.[1,2] Other distinct autosomal dominant developmental disorders have been associated with the TP63 gene, including Rapp-Hodgkin syndrome (RHS; OMIM 129400), ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome (EEC syndrome; OMIM 604292), acro-dermato-ungual-lacrimal-tooth syndrome (ADULT syndrome; OMIM 103285), limb-mammary-syndrome (LMS; OMIM 603543) and split hand/foot malformation syndrome (SHFM syndrome; OMIM 605289). As clinical and even molecular features commonly overlap, it has been proposed that some of these syndromes represent a variable spectrum of the same genetic disorder.[3]

A 57-year-old woman with a personal history of numerous ophthalmologic surgical procedures was referred to her ophthalmologist for a biopsy of buccal mucosa to rule out cicatricial pemphigoid. Physical examination revealed patchy alopecia of the scalp, eyebrows and eyelids (Figure 1), nail dystrophy, hypodontia and hypohidrosis, all these conditions present since childhood or birth. Furthermore, there was a decreased eye diameter and a tendency to adhesion of the ciliary edges of the eyelids. This situation caused severe photosensitivity (Figure 2). More recently, the patient presented palmoplantar hyperkeratosis. Neither cleft lip nor palate was present.

Diagnosis of ectodermal dysplasia syndrome was proposed, more specifically of Hay-Wells (AEC) syndrome. A punch biopsy specimen from the scalp revealed the presence of rudimentary hair structures, some of which gave rise to *vellus type* hair, and total absence of sebaceous glands (Figure 3).

The patient was offered genetic testing and was found to have an heterozygous Arg243Trp mutation in the TP63 gene (c.727C>T), which was previously reported in the *Human Gene Mutation Database* only associated with a phenotype of EEC syndrome, but never with a phenotype of AEC syndrome. Genetic counselling in family members was offered on several occasions but the patient always refused.

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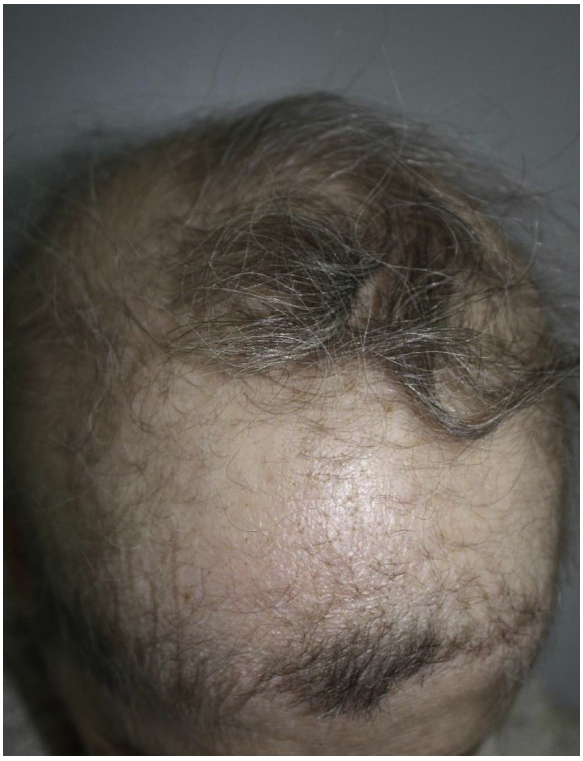

Figure 1 The patient presented congenital wiry, sparse, pale hair on the scalp, eyebrows and eyelids, due to ectodermal dysplasia.

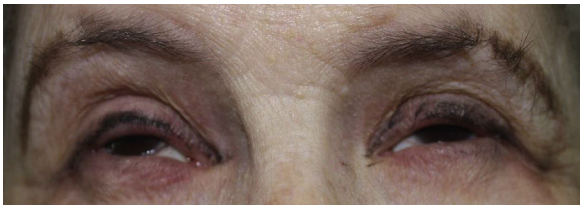

Figure 2 Due to the presence of congenital ankyloblepharon, the patient had undergone numerous eye procedures. At the time of consultation she presented severe photosensitivity. Patchy alopecia affecting eyebrows and eyelids can also be seen in this photo.

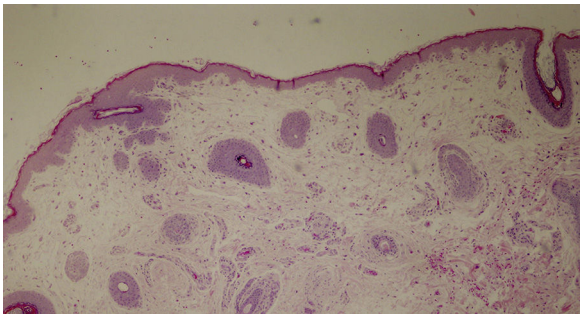

Figure 3 Skin biopsy specimen from the scalp showing the presence of rudimentary hair structures and total absence of sebaceous glands, co ncordant with ectodermal dysplasia.

The TP63 gene is a member of the TP53 gene family that encodes for p63, a key molecule in craniofacial and limb development, skin differentiation and carcinogenesis. Its structure comprises five domains, including transactivation domain, DNA-binding domain, oligomerization domain, sterile-alpha-motif (SAM) domain and the transactivation inhibitors domain. Tp63 mutations associating ectrodactily are usually located in the DNA-binding domain, as occurs in EEC syndrome, whereas AEC syndrome and other mutations without ectrodactily are mostly caused by mutations in the p63 SAM domain.[4–6] Mutations in DNA-binding domain associated with a phenotype of AEC syndrome are very seldom reported, as in the case described here, so these mutations must remain under ''uncertain significance''.

Clinical variability is one of the hallmarks of AEC syndrome.[4] The major symptoms include congenital ectodermal dysplasia with coarse, wiry, sparse hair; dystrophic nails; slight hypohidrosis; scalp infections; ankyloblepharon filiforme adnatum; hypodontia; maxillary hypoplasia; and cleft lip/palate. Other features include palmoplantar hyperkeratosis, broad nose, skin pigmentation disorder or ear deformities.[1,7,8]

The main differential diagnosis must be established with RHS and EEC syndrome. AEC syndrome differs from the other TP63 mutation-related conditions in the severity of skin phenotype, absence of ectrodactyly and, especially, the occurrence of ankyloblepharon. Cleft lip/palate is also a feature of AEC syndrome that is shared with EEC syndrome, RHS and LMS, but not with ADULT syndrome, and it is not typical of SHFM.

It has been proposed that RHS and AEC syndrome represent a variable spectrum of the same genetic disorder,[3,9] as they overlap in clinical and molecular features, as reported in some of the cases of both entities sharing the same mutations. The only phenotypic variation between the two syndromes is ankyloblepharon, which is present in over 58% of reported cases of AEC syndrome.[3]

The presence of ectodermal dysplasia associated with ankyloblepharon has been reported in other syndromes such as CHANDS (curly hair-ankyloblepharon-nail dysplasia syndrome) and Rosselli-Giulienetti syndrome that should be considered in the differential diagnosis of AEC syndrome, although its mode of inheritance is autosomal recessive.[10]

Treatment of AEC syndrome focuses on the symptoms present. Genetic counselling is helpful for the individual and family affected. The prognosis of patients with AEC syndrome is favourable, with progressive improvement of cutaneous lesions.[7,8]

In conclusion, we report a case of AEC syndrome presenting a mutation previously only associated with a phenotype of EEC syndrome, suggesting that all TP63-related disorders may be a result of phenotypic variability within a spectrum of a single genetic condition.

Bibliografía

1. Rosa DJ, Machado RF, Martins Neto MP, Sá AA, Gamonal A. Hay-Wells syndrome: A case report. An Bras Dermatol. 2010;85:232–5.

2. Celik TH, Buyukcam A, Simsek-Kiper PO, Utine GE, Ersoy-Evans S, Korkmaz A, et al. A newborn with overlapping features of AEC and EEC syndromes. Am J Med Genet A. 2011;155A:3100–3.
3. Clements SE, Techanukul T, Holden ST, Mellerio JE, Dorkins H, Escande F, et al. Rapp-Hodgkin and Hay-Wells ectodermal dysplasia syndromes represent a variable spectrum of the same genetic disorder. Br J Dermatol. 2010;163:624–9.
4. Macias E, de Carlos F, Cobo J. Hay-Wells syndrome (AEC): A case report. Oral Dis. 2006;12:506–8.
5. Garcia Bartels N, Neumann LM, Mleczko A, Rubach K, Peters H, Rossi R, et al. Hay-Wells syndrome in a child with mutation in the TP73L gene. J Dtsch Dermatol Ges. 2007;5:919–23.
6. Melino G, Lu X, Gasco M, Crook T, Knight RA. Functional regulation of p73 and p63: Development and cancer. Trends Biochem Sci. 2003;28:663–70.
7. Nagaveni NB, Umashankara KV. Hay-Wells syndrome of ectodermal dysplasia: A rare autosomal dominant disorder. Indian J Hum Genet. 2011;17:245–6.
8. Khalfi L, Hamama J, Mahroug L, Arrob A, Sabani H, El Khatib K. Hay-Wells syndrome: A case report. Arch Pediatr. 2016;23:163–6 [Article in French].
9. Kannu P, Savarirayan R, Ozoemena L, White SM, McGrath JA. Rapp-Hodgkin ectodermal dysplasia syndrome: The clinical and molecular overlap with Hay-Wells syndrome. Am J Med Genet A. 2006;140:887–91.
10. Martínez-Frías ML, Martín Bermejo M, Ayala Garcés A, Pardo Romero M, Bermejo Sánchez E, Urioste Azcorra M. The Hay-Wells syndrome, its incidence in Spain and a review of the literature. An Esp Pediatr. 1996;45:101–4 [Article in Spanish].

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Primary Cutaneous Mucormycosis Due to *Rhizopus arrhizus* in an 8-Year-Old Girl☆

Mucormicosis cutánea primaria por *Rhizopus arrhizus* en una niña de 8 años

To the Editor:

An 8-year-old girl with a personal history of severe epileptiform encephalopathy was admitted to the pediatric intensive care unit for epileptic status with decreased consciousness, for which treatment with anticonvulsants and systemic corticosteroids was instituted. Two weeks after admission she underwent assessment at the dermatology department for lesions on the abdomen that had appeared a few hours earlier. Erythematous and purpuric papules and pseudovesicles were clustered irregularly on an erythematous base with a necrotic center (Fig. 1A). An underlying firm, infiltrated plaque covered an area greater than that of the visible lesions. Ultrasound showed a poorly defined mass of increased echogenicity in the subcutaneous tissue that was compatible with inflammatory alterations. Given the acute course and the presence of an underlying mass, a deep biopsy was performed, revealing the presence of foul-smelling fatty tissue with a putrefied appearance (Fig. 1B), suggestive of a necrotic infection. A sample was taken for microbiological analysis and calcofluor-white staining and fungal culture were ordered. Direct observation revealed the presence of numerous broad, branched, aseptate hyphae compatible with mucormycosis (Fig. 2). After extensive early surgical resection liposomal amphotericin B treatment was instituted and corticosteroid treatment gradually withdrawn. Histology revealed intense dermal necrosis and blood vessel obstruction by numerous fungal structures (Fig. 3). Diagnosis was confirmed based on the results of the fungal culture, from which *Rhizopus arrhizus* was isolated following ethanol-formic acid extraction and MALDI-TOF (matrix-assisted laser desorption/ionization – time-of-flight) mass spectrometry.[1] After lesion spread was ruled out the patient was diagnosed with primary cutaneous mucormycosis due to *R. arrhizus*. The early initiation of treatment resulted in a favorable response and progressive improvement of the patient's clinical picture. No new lesions appeared nor were other organs affected.

Mucormycosis is an opportunistic fungal infection with a rapid, fulminant course caused by fungi of the order Mucorales. The most frequently isolated fungi are those of the genera *Rhizopus*, *Mucor*, and *Rhizomucor*.[2] There is some debate as to whether this group of infections should be described as zygomycosis or mucormycosis, but use of the latter term is supported by the results of molecular studies.[3]

Distinct clinical forms of mucormycosis are described. The most common is rhinocerebral mucormycosis, followed by pulmonary, gastrointestinal, cutaneous, and disseminated forms. The cutaneous form (10%–19% of cases) is the result of direct inoculation of the spores into the dermis or direct contact of the skin with contaminated material.[4] It can also be caused by traumatic injuries (70%), surgical interventions (15%), burns (3%), and, in the case of nosocomial infections, contact with contaminated material such as sheets,[5] intravenous lines, adhesives,[6] or wooden tongue depressors.[7]

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