

However, some of these patients develop SCARs related to sorafenib, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), SJS or AGEP.<sup>5,6,8,9</sup>

To our knowledge, only 2 more cases of sorafenib-induced acute exanthematous pustulosis have been published, being one of them an acute localized exanthematous pustulosis (ALEP) and the other one a complete AGEP.<sup>5,6</sup> The main features of these cases are presented in Table 1. Interestingly, all the three cases occurred in women who were under treatment with sorafenib due to unresectable hepatocarcinoma. Cases of AGEP have also been reported associated with other multikinase inhibitors such as imatinib.<sup>10</sup> Therefore; we believe that the association between kinase-inhibitors and AGEP might be an under-reported entity with an increasing incidence due to the appearance of new drugs of this nature.

In conclusion, we report a new case of sorafenib-induced AGEP. We should be aware of this cutaneous side effect of sorafenib and other multikinase inhibitors, given that drug discontinuation is the key point on AGEP treatment.

### Conflict of interests

The authors declare no conflict of interest.

### References

1. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): a review and update. *J Am Dermatol*. 2015;73:843–8.
2. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP): a clinical reaction pattern? *J Cutan Pathol*. 2001;28:113–9.
3. Horcajada-Reales C, Pulido-Pérez A, Suárez-Fernández R. Toxicodermias graves: ¿existen las formas combinadas? *Actas Dermo-sifiliográficas*. 2016;107:23–33.

4. Robert C, Mateus C, Spatz A, Wechsler J, Escudier B. Dermatologic symptoms associated with the multikinase inhibitor sorafenib. *J Am Dermatol*. 2009;60:299–305.
5. Liang CP, Yang CS, Shen JL, Chen YJ. Sorafenib-induced acute localized exanthematous pustulosis in a patient with hepatocellular carcinoma. *Br J Dermatol*. 2011;165:443–5.
6. Pretel M, Iñarrairaegui M, Lera JM, Aguado L, Idoate MA. Acute generalized exanthematous pustulosis induced by sorafenib. *JAMA Dermatol*. 2014;150:664–6.
7. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer. Part II. Targeted therapies. *J Am Dermatol*. 2014;71:217.e1–11.
8. Kim DK, Lee SW, Nam HS, Jeon DS, Park NR, Nam YH, et al. A case of Sorafenib-induced DRESS syndrome in hepatocellular carcinoma. *Korean J Gastroenterol*. 2016;67:337–40. <http://dx.doi.org/10.4166/kjg.2016.67.6.337>.
9. Sohn KH, Oh SY, Lim KW, Kim MY, Lee SY, Kang HR. Sorafenib induces delayed-onset cutaneous hypersensitivity: a case series. *Allergy Asthma Immunol Res*. 2015;7:304–7. <http://dx.doi.org/10.4168/aaair.2015.7.3.304>.
10. Scott AD, Lee M, Kubba F, Chu A. Acute generalized exanthematous pustulosis (AGEP) secondary to imatinib in a patient with chronic myeloid leukaemia. *Clin Exp Dermatol*. 2015;40:926–7.

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## Expanding the Genotype of Sjögren–Larsson Syndrome: A New Case Due to Two Novel Mutations



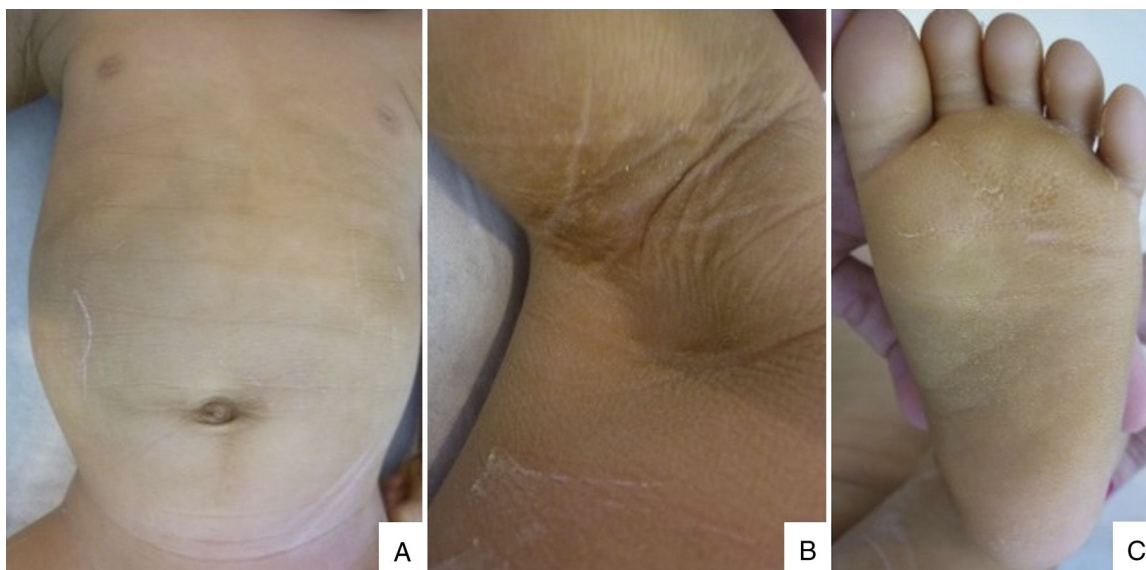
### Ampliando el genotipo del síndrome de Sjögren-Larsson: un nuevo caso causado por dos nuevas mutaciones

Dear Editor,

Sjögren–Larsson syndrome (SLS) is a rare genetic disorder with autosomal recessive inheritance,<sup>1,2</sup> characterized by clinical triad of congenital ichthyosis, spastic diplegia or tetraplegia and mental retardation.<sup>1,3,4</sup> We report a new patient affected by SLS due to two unreported mutations.

A 6 months male child was referred to our hospital because of congenital erythroderma and subsequent development of generalized fine scaling and persistent pruritus. He was the first child of non-consanguineous parents, born

at 33 weeks of gestation. There was no history suggestive of a collodion membrane at birth, and no family history of ichthyosis. On physical examination we observed generalized fine desquamation on the limbs and trunk without underlying erythema (Fig. 1A) and hyperkeratotic skin on the armpits (Fig. 1B), palms and soles (Fig. 1C). Hair and nails appeared normal. Given that an ichthyosis was the diagnosis suspected, a skin biopsy from an armpit was made. Histological study showed hyperkeratosis, psoriasiform epidermal hyperplasia, a prominent granular layer in some areas of the epidermis and mild perivascular inflammatory infiltrate of mononuclear cells in papillary dermis (Fig. 2), resulting compatible with a congenital ichthyosis. The rest of the physical exam showed the patient had macrocephaly, mild psychomotor retardation, mild axial hypotonia, incipient signs of spasticity in the lower limbs, and occasional spasms. A transfontanelar ultrasound showed benign external hydrocephaly, which was confirmed in a brain magnetic resonance imaging where others anomalies were not observed. Given the coexistence of congenital ichthyosis and neurological signs, our clinical suspicion was a neurocutaneous disorder.



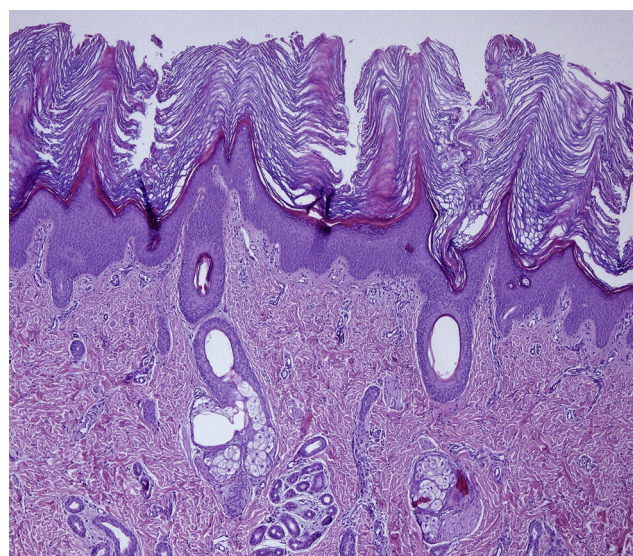
**Figure 1** (A) Generalized xerosis with fine desquamation on the trunk. (B) Hyperkeratotic and brownish skin on the armpits. (C) Hyperkeratotic skin on the soles.

Ophthalmologic examination, peripheral blood smear, peripheral blood analysis and abdominal ultrasound were normal. Genetic analysis of the patient confirmed the diagnosis of Sjögren-Larsson syndrome (SLS) by identifying two unreported heterozygous ALDH3A2 mutations, a deletion mutation c.154\_155delAG (p.Ser52Stop) in exon 2 and a missense mutation c.536A>T (p.Asp179Val) in exon 4. The c.154\_155delAG mutation is considered of pathogenic nature, and the variant c.536A>T is likely to cause disease by several in silico analysis. Despite the genetic counseling, the patient's parents did not want to perform the genetic study in that moment. Progressively, the neurological symptoms were worsening by detecting hyperreflexia, spasticity and delay speech in our patient.

In 1957, Karl Gustaf Torsten Sjögren, on collaboration with Tage K. Larsson, established the clinical and genetic profile of the Sjögren-Larsson syndrome (SLS).<sup>5</sup> SLS is a recessively inherited neurocutaneous disorder characterized by a triad of congenital ichthyosis, mild to moderate mental retardation and spastic diplegia or tetraplegia, caused by a fatty aldehyde dehydrogenase (FALDH) deficiency.<sup>4,6,7</sup> It occurs in all races and its prevalence worldwide has been estimated as 0.4:100,000 live births.<sup>1,4</sup>

SLS is caused by mutation in the ALDH3A2 gene on the short arm of chromosome 17 (17p11.2), that is the gene for FALDH which catalyzes oxidation of long chain aliphatic alcohols to corresponding fatty acids.<sup>3,8</sup> The consequent accumulation of fatty aldehyde precursors, including fatty alcohols, caused by the FALDH deficiency, is postulated to affect the normal formation of multilamellar membranes in the stratum corneum and myelin, and to result in the symptoms.<sup>7</sup>

The disorder presents at birth or in the neonatal period with varying degrees of erythema and ichthyosis, but a collodion membrane is rarely seen. Ichthyosis has a generalized distribution across the trunk, flexures and nape of neck, although the central face is spared in most cases.<sup>1</sup> Palmo-



**Figure 2** A skin biopsy from an armpit revealed hyperkeratosis, psoriasiform epidermal hyperplasia and slightly thickened granular layer in epidermis, and mild perivascular inflammatory infiltrate of mononuclear cells in papillary dermis (H&E 4×).

plantar keratoderma is seen in 50% of cases.<sup>3</sup> The nails and hair are interestingly normal.<sup>6</sup> Persistent pruritus is common, which is mostly absent in other forms of ichthyosis.<sup>1,4,8</sup> The histological findings of hyperkeratosis, papillomatosis, acanthosis, and a mildly thickened granular layer are nonspecific.<sup>5</sup>

The diagnosis of SLS is delayed until the onset of neurological symptoms, because only cutaneous manifestations are present at birth.<sup>3</sup> The neurological symptoms appear in the first or second year of life,<sup>3,4</sup> and include cognitive impairment, brain magnetic resonance imaging (MRI) findings, speech-language development and spasticity.<sup>1</sup> One-third of patients present with perifoveal glistening

white dots in the ocular fundus which appear after several years of age,<sup>3</sup> and their occurrence strongly suggests SLS.<sup>4</sup> Macrocephaly is not a characteristic or common finding in SLS.

Mutation analysis of the ALDH3A2 gene is a highly sensitive method of confirming the diagnosis of SLS.<sup>4</sup> More than 90 pathogenic variants of ALDH3A2 have been identified to date.<sup>1</sup> The diagnosis of SLS can be confirmed by measurement of enzyme activity in cultured skin fibroblasts or leukocytes.

There is no permanent cure for SLS and no specific therapy, so that a multidisciplinary approach is necessary.<sup>3</sup>

In conclusion, we report a new case of SLS caused by two novel mutations, supporting the rich mutational heterogeneity associated with this syndrome. High index of suspicion is necessary for the diagnosis of SLS, so that in a neonate or infant with congenital ichthyosis and neurological symptoms we must rule out this neurocutaneous disorder.

### Conflict of interests

The authors declare no conflict of interest.

### References

1. Gaboon NE, Jelani M, Almramhi MM, Mohamoud HS, Al-Aama JY. Case of Sjögren–Larsson syndrome with a large deletion in the ALDH3A2 gene confirmed by single nucleotide polymorphism array analysis. *J Dermatol*. 2015;42:706–9.
2. Gånemo A, Jagell S, Vahlquist A. Sjögren-Larsson syndrome: a study of clinical symptoms and dermatological treatment in 34 Swedish patients. *Acta Derm Venereol*. 2009;89:68–73.
3. Srinivas SM, Raju KV, Hiremagalore R. Sjögren-Larsson syndrome: a study of clinical symptoms in six children. *Indian Dermatol Online J*. 2014;5:185–8.
4. Incecik F, Herguner OM, Rizzo WB, Altunbasak S. A Turkish family with Sjögren–Larsson syndrome caused by a novel ALDH3A2 mutation. *Ann Indian Acad Neurol*. 2013;16:425–7.
5. Aboud KA, Aboud DA. Karl Gustaf Torsten Sjögren and Sjögren–Larsson syndrome. *Dermatol Reports*. 2011;3:e34.
6. Yiş U, Terrinoni A. Sjögren-Larsson syndrome: report of monozygote twins and a case with a novel mutation. *Turk J Pediatr*. 2012;54:64–6.
7. Botelho Gomes JM, Vieira AP, Navarro J, Maré R, Tavares P, Brito C. Sjögren–Larsson syndrome due to a novel mutation in the FALDH gene. *Eur J Dermatol*. 2011;21:412–3.
8. Gupta SP, Mittal A, Maini B, Gupta S. Sjögren–Larsson syndrome: a case report of a rare disease. *Indian Dermatol Online J*. 2011;2:31–3.

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## Split doses of Methotrexate in patients with moderate to severe Psoriasis



### Dosis divididas de metotrexato en pacientes con psoriasis moderada a severa

Dear Editor,

Psoriasis is the most common inflammatory skin condition with a worldwide prevalence of 2%. Systemic or topical treatment is decided according to the severity of the disease.<sup>1</sup> For systemic treatment, Methotrexate (MTX) remains effective and medically accessible: it is widely used in hospitals in Latin America, where biological therapy is still limited for economic reasons.<sup>2</sup>

The article: "Methotrexate in Moderate to Severe Psoriasis: Review of the Literature and Expert Recommendations"<sup>3</sup> outlines very important and interesting recommendations on the use of this drug in Psoriasis. However, one point that has not been taken into account is the split of MTX in two or three weekly doses, with the benefit of both efficacy and reduced side effects.

The benefits of fractional doses are listed below. As indicated in the article, MTX has significant gastrointestinal

adverse effects that hinder its use, and increases with higher oral doses; but can be avoided or reduced with parenteral route, and with folates.<sup>3</sup> In addition, a divided dose of MTX is an alternative for reducing gastrointestinal side effects in patients with Psoriasis.<sup>4</sup> Second, with high MTX enteral doses, bioavailability decreases (for limiting absorption); therefore it is beneficial to divide MTX into smaller doses and thus increase its concentration systemically,<sup>5</sup> increasing efficiency without worsening adverse effects.<sup>6</sup>

Although MTX experience with divided doses for Psoriasis has been well known and accepted<sup>7</sup> for several decades,<sup>8</sup> it is based on a limited number of studies.<sup>5,9</sup> Thus, further experience with divided doses of MTX has been carried out in rheumatologic patients, but these are also limited.

Weinstein and Frost<sup>9</sup> first proposed the divided dose of MTX for Psoriasis in 1971. They showed that small doses of 2.5–7.5 mg of MTX given at intervals of 12 h for a total of three doses every week had an improvement from 75% to 100% in 26 patients with severe Psoriasis, with minimal adverse effects (nausea, oral ulcers and hives).

Chladek et al.<sup>5</sup> conducted a study that related the pharmacodynamics and pharmacokinetics of divided doses (2.5 mg and 5 mg three times a week) and weekly full doses (7.5 mg and 15 mg) of MTX with the Psoriasis Area Severity Index of 41 patients with severe disease. They concluded that split doses of MTX were associated with greater efficacy