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CASE AND RESEARCH LETTERS

Dyshidrotic Eczema Secondary to Intravenous Immunoglobulin Infusion: A Report of 2 Cases☆

Eccema dishidrótico secundario a la infusión de inmunoglobulinas intravenosas: presentación de 2 casos

Letter to the Editor:

We present 2 cases of dyshidrotic eczema secondary to intravenous immunoglobulin infusion. The first patient was a 58-year-old man who had been diagnosed with Guillain-Barré syndrome after presenting with sock-like paresthesia, unstable gait, and diminished tendon reflexes. The patient was treated with intravenous immunoglobulin, and his symptoms gradually improved. Ten days after admission, he began to develop asymptomatic lesions on his palms and soles.

Physical examination revealed punctate vesicular lesions filled with clear fluid on an erythematous base located bilaterally on the palms and soles (Fig. 1). Some of the vesicular lesions were purpuric in appearance and filled with blood, especially in dependent parts of the body (Fig. 2). No mucosal involvement or lesions at other sites were observed.

Histopathology revealed an epidermis with psoriasiform hyperplasia, lymphocytic and erythrocytic exocytosis, and extensive spongiosis with formation of large subcorneal vesicles. The underlying dermis showed a moderate superficial perivascular lymphohistiocytic inflammatory infiltrate accompanied by blood extravasation.

The second patient was a 67-year-old man whose personal history included removal of pleomorphous sarcoma on the right pectoral muscle and treatment with radiotherapy and chemotherapy. He was admitted 8 months after surgery for assessment of ataxia. During admission, and given the gradual worsening of his condition, he received intravenous immunoglobulin, and his symptoms partially resolved.

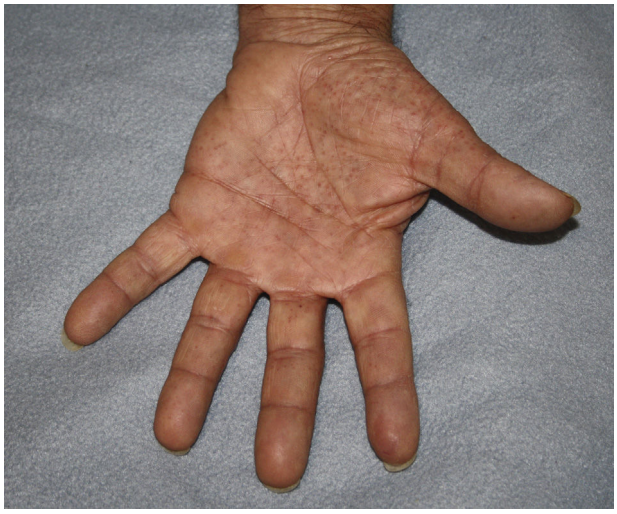

Figure 1 Vesicular lesions on an erythematous base on the palm of the first patient.

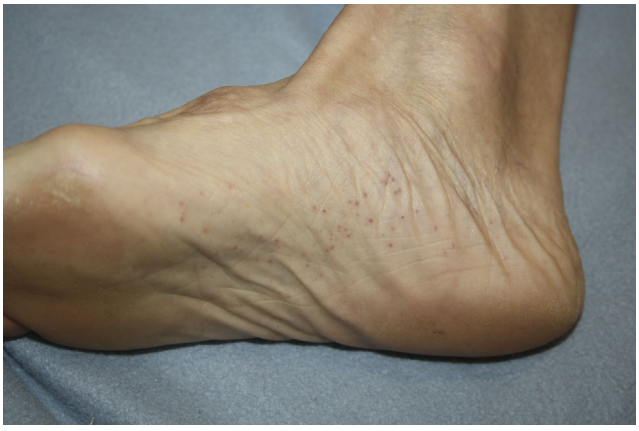

Figure 2 Vesicular blood-filled lesions on the sole of the first patient.

A dermatological evaluation was ordered for the asymptomatic skin lesions, which were very similar to those of the first patient: vesicular lesions filled with clear fluid on an erythematous base located on the palms and soles.

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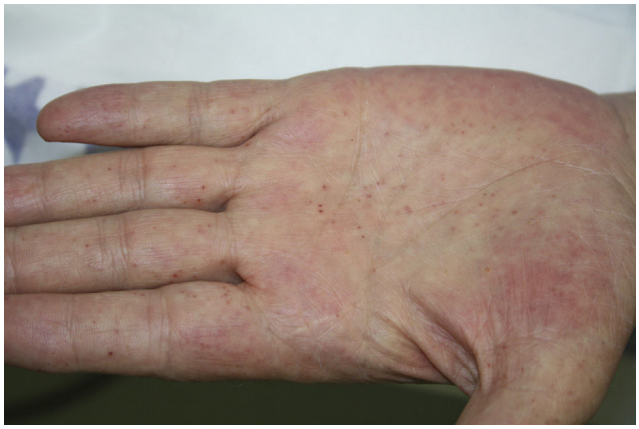

Figure 3 Vesicular lesions on an erythematous base on the palm of the second patient.

Histopathology findings were very similar to those of the first patient (Fig. 3).

We diagnosed both patients with dyshidrotic eczema secondary to treatment with intravenous immunoglobulin.

The lesions resolved in both cases with topical corticosteroids, although they reappeared in the first patient during the second cycle of treatment.

Intravenous immunoglobulins are isolated from plasma obtained from between 1000 and 100 000 persons. They are subsequently purified to eliminate or inactivate infectious agents and prevent the formation of aggregates.[1] They have been approved by the European Medicines Agency for the following indications: primary immunodeficiency syndromes with impaired antibody production; hypogammaglobulinemia and recurrent bacterial infections in patients with chronic lymphocytic leukemia in which antibiotic prophylaxis has not been successful; hypogammaglobulinemia and recurrent bacterial infection in patients with plateau-phase multiple myeloma who did not respond to pneumococcal vaccination; hypogammaglobulinemia in patients who undergo allogenic stem cell transplantation; congenital AIDS with recurrent bacterial infection; primary immune thrombocytopenia; patients at high risk of bleeding; patients undergoing surgery to correct their platelet count; Guillain-Barré syndrome; and Kawasaki disease.[2] They are used off-label in numerous hematologic, neurologic, rheumatologic, infectious, and dermatologic conditions.[1]

Intravenous immunoglobulin has a good safety profile, and most adverse effects are associated with administration. The adverse effects, which are immediate, mild, and transient, consist of flulike symptoms that include headache, flushing, general malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnea, back pain, nausea and vomiting, diarrhea, changes in blood pressure, and tachycardia. The most severe adverse effects are usually late in onset and manifest as thromboembolic events and renal, neurologic, and/or hematologic toxicity. Cutaneous adverse effects appear in 0.4%-6% of patients in the form of transient urticaria or maculopapular rash, palmar pruritus, hair loss, erythema multiforme, erythematous purpuric rash, petechiae on the limbs, ulceration of the oral mucosa, transient epidermolysis bullosa, lichenoid eruptions, and Baboon syndrome.[3]

Eczema is rarely associated with administration of intravenous immunoglobulin. In their review of the literature, Gerstenblith et al.[4] found 64 patients with eczematous reactions associated with intravenous immunoglobulin. The most common findings were the presence of multiple punctate erythematous vesicles grouped together on the palms and soles. Histopathology revealed the spongiotic loculated vesicles that are typical of dyshidrosis and a perivascular infiltrate composed of lymphocytes and eosinophils, as well as lymphocytic exocytosis in the epidermis. Overall, 62.5% of patients had lesions of dyshidrotic eczema on the palms and soles or on the palms and soles and at least 1 other affected site. Most patients received intravenous immunoglobulin for neurologic diseases. Almost all patients responded well to topical corticosteroids or did not require treatment, although treatment with oral corticosteroids was occasionally necessary. The eczematous reaction improved in all the cases reported, although in 1 case, itching persisted for months after suspending intravenous immunoglobulins. Despite these findings, therapy was suspended because of the eczematous reactions. No clear mechanism has been identified that might explain the association with eczema,[4] although some authors suggest a hypersensitivity reaction to the drug or vehicle that has not been demonstrated with patch testing or prick testing.[5]

In the first patient, we thought that the skin lesions were gloves and socks syndrome, given that the histopathology findings were consistent with this syndrome and that this and Guillain-Barré syndrome can be triggered by common infectious agents such as parvovirus, *Mycoplasma*, Epstein-Barr virus, and cytomegalovirus[6,7]; however, the results of serology testing to various pathogens were repeatedly negative.

Other diseases that can be taken into consideration with this type of lesion include palmoplantar pustular psoriasis, allergic contact dermatitis, dyshidrosiform tinea, scabies, id reaction, herpes simplex, and other bullous diseases such as pemphigus, pemphigoid, and epidermolysis bullosa.[5]

As this was a first episode of asymptomatic lesions associated in time with infusion of intravenous immunoglobulin (8 and 5 days, respectively) and reappearance of the lesions during the second treatment cycle in the first patient, we were able to confirm the diagnosis.

References

1. Looney RJ, Huggins J. Use of intravenous immunoglobulin G (IVIG). Best Pract Res Clin Haematol. 2006;19:3–25.
2. [consultado 10 Sept 2015] Available at: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000781/WC500023473.pdf
3. Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous immunoglobulin: Adverse effects and safe administration. Clin Rev Allergy Immunol. 2005;29:173–84.
4. Gerstenblith MR, Antony AK, Junkins-Hopkins JM, Abuay R. Pompholyx and eczematous reactions associated with intravenous immunoglobulin therapy. J Am Acad Dermatol. 2012;66:312–6.

5. Lofgren SM, Warshaw EM. Dyshidrosis: Epidemiology, clinical characteristics, and therapy. Dermatitis. 2006;17:165–81.
6. Pemira SM, Tolan RW Jr. Mycoplasma pneumoniae infection presenting as bullous papular purpuric gloves and socks syndrome: Novel association and review of the literature. Clin Pediatr (Phila). 2011;50:1140–3.
7. Winer JB. An update in Guillain-Barré syndrome. Autoimmune Dis. 2014;2014. ID793024.

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Self-healing Collodion Baby: A New Mutation in the *ALOX12B* Gene☆

Bebé colodión autorresolutivo: nueva mutación en el gen ALOX12B

Dear Editor:

We present the case of a newborn infant born preterm at 36 weeks, with no family history of interest, diagnosed in utero with eclabium and ectropion, with a suspected diagnosis of harlequin fetus. At birth, the infant presented a membrane that covered practically the whole body surface like a suit of armor (Fig. 1A), in addition to ectropion, eclabium, clawed-hand deformity (Fig. 1B), and retraction of the auricles of both ears (Fig. 1C). During the first days after delivery, the membrane fissured and subsequently peeled away in large sheets (Fig. 1D), leaving the underlying skin erythematous and exudative; the membrane had fallen completely by the second week of life. The clinical course was very good over the following months, and at 1 year the skin had a practically normal appearance (Fig. 2A), showing only mild erythema and peeling on both cheeks (Fig. 2B) and minimal hyperkeratosis on the elbows and knees. A diagnosis of self-healing collodion baby (CB) was made. Genetic analysis showed the child to be a homozygous carrier of a mutation in the *ALOX12B* gene that produced loss of an amino acid, glutamine, at position 136 of exon 3; the parents were healthy heterozygous carriers of this mutation. At the time of writing this article, the patient was 2 years of age and had no lesions except those commented above.

CB presents at birth with a tight, shiny, transparent, armor-like membrane that covers the whole body surface and looks like cellophane wrapping.[1,2] This can give rise to ectropion, eclabium, pseudocontractures, absence of eyebrows, sparse hair, and hypoplasia of the nasal and auricular cartilage.[1,2] The membrane is inelastic, so the child's breathing and movements after birth provoke fissuring, and it then peels away in large sheets and is completely lost by 2 to 4 weeks of life.[3] CB is a rare condition, with an incidence between 1 in 50 000 to 1 in 100 000 births. It is the initial clinical manifestation of a number of genetic diseases, the majority of which belong to the group of autosomal recessive congenital ichthyoses (ARCI).[4] CB can develop into very diverse phenotypes, from skin with a normal appearance to intense ichthyosis; the majority of patients are diagnosed with lamellar ichthyosis or congenital ichthyosiform erythroderma.[1,3] Self-resolving CB is a minor form of ARCI.[4] Between 10% and 24% of cases of CB are self-resolving; these are cases that show spontaneous resolution of the condition and in adult life present a normal skin or discreet signs of ichthyosis.[1,5] Regarding the epidemiology of ARCI, Hernández-Martín et al., in Spain, published a study in which the estimated prevalence of ARCI was of approximately 16 cases per million population, with a prevalence of self-resolving CB of 4.2% in the overall ARCI population.[6]

Self-resolving CB has been associated with mutations in genes *TGM1*, *ALOXE3*, and *ALOX12B*.[1,3–5,7] Our patient was diagnosed as a homozygous carrier of a mutation in gene *ALOX12B* that has not previously been described in the literature. The *ALOX12B* gene was first identified in 2002. It is formed of 15 exons and codes for the epidermal lipoxygenases eLOX-3 and 12R-LOX.[8] Its predominant expression in the suprabasal layers of the epidermis supports its role in the advanced phases of epidermal differentiation and its participation in processing lamellar bodies. In addition, it acts in the hepoxilin pathway and is therefore thought possibly to participate in the formation of the intercellular lipids of the corneal layer or to act in signaling to promote keratinocyte differentiation.[8]

More than 30 mutations of the *ALOX12B* gene have been described since its identification and, together with gene *ALOXE3*, it is considered responsible for 14% to 17% of ARCIs and for 72.2% of cases of self-resolving CB.[8] The specific mechanism that leads to the changes in skin permeability in patients with alterations of gene *ALOX12B*, and the reason for the appearance of lesions in the neonatal period in self-resolving CB, are not fully understood.[7] It has been postulated that these mutations of *ALOX12B* reduce enzyme activity in utero, but not after birth.[8] Hydrostatic pressure is high in the uterus, and the chelation of water molecules deforms the mutated enzyme into an inactive conformation. After birth, with a lower hydrostatic pressure, the enzyme returns to its active form and increases its activity to levels sufficient to maintain a normal or minimally altered phenotype.[8,9]

CB usually causes premature delivery, with increased perinatal morbidity and mortality. Important complications include increased transepidermal water loss (up to 7 times the loss from healthy skin), temperature instability, hypothermia, hypernatremic dehydration, feeding difficulties, hypohidrosis, cutaneous and systemic infections, ectropion, keratitis, and obstruction of the external auditory meatus.[1,2,5,10] Furthermore, the membrane can

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