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LETTER TO EDITOR

Interleukin-36 Receptor Antagonist Deficiency (DITRA) with a Novel IL36RN Homozygous Mutation c.200G > T (P.Cys67Phe) in a Young Colombian Woman

Andres F. Zea-Vera[1,2] · Felipe E. Estupiñan-Lopez[3] · Jaqueline Cifuentes-Burbano[3] · Myriam J. Vargas[3,4] · Anilza Bonelo[1]

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To the editor,

Generalized pustular psoriasis (GPP) is an unusual clinical presentation of pustular psoriasis. The acute variant of generalized pustular psoriasis or Von Zumbusch psoriasis is characterized by the abrupt onset of numerous pustules, widespread erythema, and systemic symptoms representing a life-threatening condition. Deficiency of interleukin-36 receptor antagonist (DITRA) is an auto-inflammatory disorder characterized by sterile inflammation of the skin and has been related to GPP. Here we report the case of a young Colombian woman with relapsing-remitting–generalized pustular psoriasis with a novel IL36RN homozygous mutation establishing the diagnosis of deficiency of IL-36 receptor antagonist (DITRA; OMIM 614204).

Case Presentation

A 19 years old Colombian female was evaluated at the outpatient psoriasis clinic in a third level hospital in the city of Cali, Colombia. The patient complained of having scaly plaques in the trunk and extremities with severe pruritus for 6 weeks, without systemic symptoms. Two weeks prior the consultation, after the use of soy cleanser (bath soap substitute) in the entire body, she presented confluent small pustules forming plaques on the pre-existing lesions affecting additionally the face without palms, plants, or nails involvement. Past medical history was only relevant for an episode of generalized exfoliative dermatitis, interpreted as toxic epidermal necrolysis (TEN) 2 years before. The patient was not evaluated by a dermatologist neither a skin biopsy was performed; this episode is reported by the patient because medical records are unavailable. She was treated with IV clindamycin for 10 days and petrolatum dressing with complete symptoms resolution after 4 weeks. She denies previous infectious triggers. Past family medical history is unavailable because the patient was adopted at birth from unknown parents.

At physical examination, hyperkeratotic erythematous lesions with pustules which coalesce forming large plaques, affecting the scalp, trunk, extremities, and face involving 90% of the total body surface (Fig. 1a) also presented lip edema, geographic tongue, ectropion, and edema in lower limbs. Asymmetry was found between the two sides of the body with smaller right breast and shorter right thigh and arm. Dermatoscopy of the skin lesions showed punctate vessels (Fig. 1d). At admission, CBC showed a mild normocytic anemia without other significative findings: Hb 10.28 g/dL, hematocrit 31.8%, MCV 83 fL, WBC 9050/uL, neutrophils 6150/uL (67.9%), lymphos 2050/uL(22.6%), monocytes 526/uL(5.8%), and platelets 45,3000/uL. Markers for chronic infections were negative (VDRL and FTAbs, HBsAg, HB anti-core abs, anti-HCV IgG, HTLV 1–2, and 4th generation HIV test). Serum immunoglobulin levels were IgG 1705 mg/dL(767–1590), IgA 387 mg/dL(61–356), IgM 70 mg/dL(37–286), and IgE 1681 IU/mL(0–100), complement C3 125 mg/dL and C4 20.9 mg/dL. C-reactive protein (CRP) was 70 mg/

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✉ Andres F. Zea-Vera
andres.zea@correounivalle.edu.co

[1] Microbiology Department, Faculty of Health, Universidad del Valle, Calle 4b #36-00 Building 120, Office 304, Cali, Colombia

[2] Clinical Immunology Clinic, Hospital Universitario del Valle, Cali, Colombia

[3] Dermatology Service, Faculty of Health, Universidad del Valle, Cali, Colombia

[4] Psoriasis and Phototherapy Clinic, Hospital Universitario del Valle, Cali, Colombia

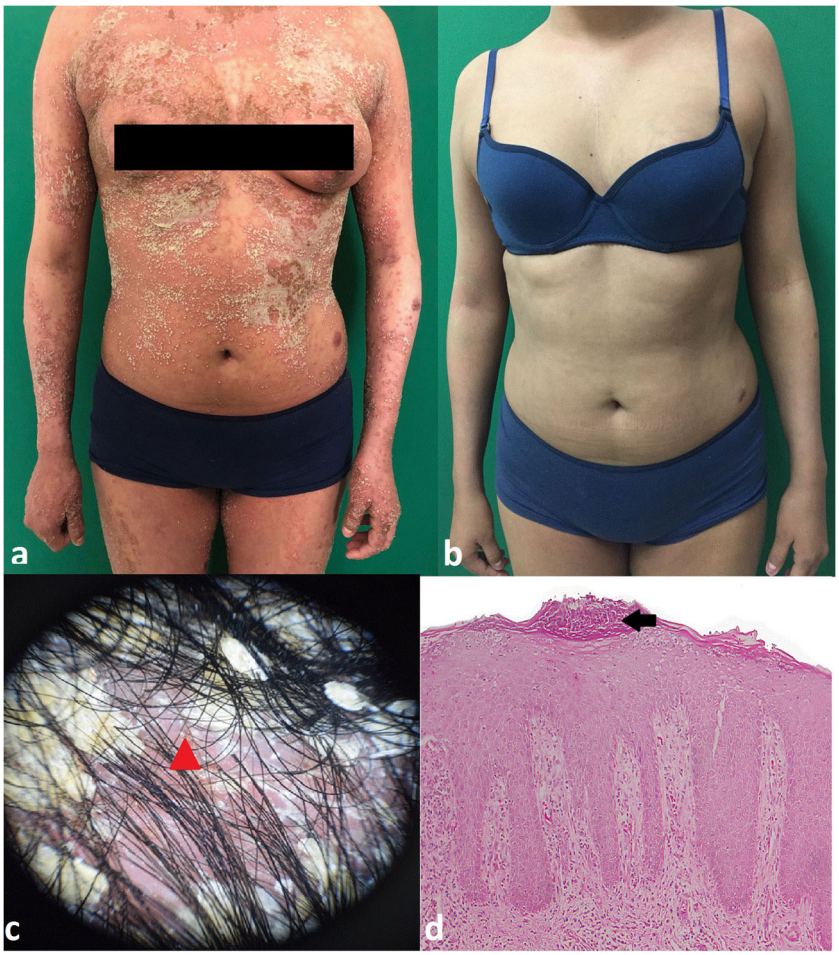

Fig. 1 Hyperkeratotic erythematous large plaques affecting 90% of body surface. (**a**) Dermatoscopy showing punctate vessels (red arrowhead) (**c**). Histopathological findings of generalized pustular psoriasis, spongiform pustule of Kogoj (black arrowhead) neutrophils infiltration into necrotic epidermis (**d**) Skin recovery after 4 weeks of treatment (**b**)

L but decreased to 16 mg/L without antibiotics after 5 days of treatment. Autoimmunity tests showed antinuclear antibodies (ANAs) positive 1/320 with a granular pattern, extractable antinuclear antibodies (ENAs), and anti-double-stranded DNA antibodies were negative.

With the diagnosis of erythroderma due to pustular psoriasis, a skin biopsy was performed, and the patient was admitted to internal medicine. Initial treatment was wet dressings with emollient and desonide 0.1% cream 2 h per day, shampoo with salicylic acid 3%, foam mometasone 0.1% on the scalp every night, and desonide 0.05% emulsion on the face every night; the patient was dewormed, and treatment using methotrexate 12.5 mg/week was initiated. Skin biopsy showed hyperkeratosis with parakeratosis, aggregates of neutrophils between degenerated, and flattened keratinocytes within the upper malpighian layer of the epidermis, forming a subcorneal macropustule (Fig. 1c). Psoriasiform changes in the epidermis with parakeratosis, elongation of the rete ridges, and focal absence of granular layer configured the diagnosis of generalized pustular psoriasis or Von Zumbush psoriasis. Acitretin (retinoid) was indicated; however, due to insurance coverage and clinical compromise, adalimumab medication was started at a dose of 80 mg followed by 40 mg every other week. Clinical immunology evaluated the patient under the hypothesis of an inborn error of immunity (primary immunodeficiency). A monogenic autoinflammatory disorder was suspected and IL36RN Sanger sequencing was done finding a novel missense mutation c.200G > T (p.Cys67Phe). Erythroderma improved after 4 weeks of adalimumab starting remaining only mild compromise in the scalp (Fig. 1b).

Discussion

To our knowledge, this is the first case of interleukin-36 receptor antagonist deficiency (DITRA) reported in South America. The genetic cause and the pathogenesis for acute generalized pustular psoriasis were unknown until 2011, when Marrakchi et al. described nine families affected by the disease with an autosomic recessive pattern and identified mutations of interleukin-36 receptor antagonist as a gene associated with the disease [1]. GPP develops as a primary condition or in association with preexisting psoriasis. However, patients, who debuted with generalized pustular psoriasis the de novo, are more likely to have *IL36RN* mutations [2] even more when its presentation is at early ages. In our case, symptoms began

at the age of 17, and no data of preexisting psoriasis was found.

In the novel homozygous missense IL36RN gene mutation, we are reporting Chr2 (GRCh37) g.113819785G > T (c.200G > T) changes cysteine by phenylalanine at position 67 of the protein. This variant is located in an evolutionarily highly conserved residue within the conserved area of IL36RN and could produce significant physicochemical changes. As an autosomal recessive disease, DITRA has been documented more frequently in consanguineous kindred [3] which cannot be assessed in this patient. A homozygous mutation with a GnomAD homozygous frequency = 0, may either be a founder mutation but assessing mutation frequency in the population cannot be done at this point. Although this homozygous mutation is classified as a variant of uncertain significance (class 3) according to the ACMG, pathogenicity predictions by most software programs including MutationTaster and PROVEAN are consistent with a potentially pathogenic variant. Clinical and histopathology findings are pathognomonic of acute generalized pustular psoriasis (Von Zumbusch psoriasis).

There is no gold standard treatment for acute GPP associated with DITRA; however, case reports and series show a good response to methotrexate, oral retinoids, anti-TNF, or IL17 inhibitors [4, 5]. The patient has started with methotrexate plus adalimumab during acute relapse (based on hospital availability), and the clinical response was outstanding. Currently, she is receiving only methotrexate 12.5 mg weekly without new relapses. To our knowledge, this is the first report of DITRA in South America, and our report highlights the necessity of molecular diagnosis and increases the awareness of inborn errors of immunity in the dermatology community in Colombia.

Compliance with Ethical Standards

Conflict of Interest The authors declared that they have no conflict of interest.

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