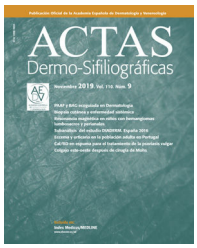
ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org



RESIDENT'S FORUM

[Translated article] RF-VEXAS Syndrome: A New Autoinflammatory Disease

FR-Síndrome VEXAS: Una nueva enfermedad autoinflamatoria

M. Fernández-Parrado[a,*], **H. Perandones-González**[b]

[a] *Servicio de Dermatología, Hospital Universitario de Navarra, Navarra, Spain*
[b] *Servicio de Dermatología, Complejo Asistencial Universitario de León, León, Spain*

KEYWORDS
VEXAS syndrome;
UBA1 gene;
Autoinflammatory disease;
Skin lesions;
Diagnosis

PALABRAS CLAVE
Síndrome VEXAS;
Gen *UBA1*;
Enfermedad autoinflamatoria;
Manifestaciones cutáneas;
Diagnóstico

VEXAS syndrome—a new autoinflammatory disease involving Vacuoles, the E-1 ubiquitin activating enzyme, X-linkage, Autoinflammation, and Somatic mutations—was first described in 2020.[1] This syndrome is caused by an acquired somatic mutation with an amino acid change (a missense mutation) in the *UBA1* gene.[1] The *UBA1* gene codes for the E-1 ubiquitin-activating enzyme needed to initiate ubiquitination, a posttranslational modification that regulates intracellular signaling and protein degradation and plays a key role in autophagy.[1] This rare entity is caused by acquired mosaic mutations of the *UBA1* gene in myeloid progenitor cells.[2]

Identifying new diseases with heterogeneous phenotypes and diverse clinical manifestations, such as autoinflammatory diseases, is a challenge. The aforementioned study, rather than grouping together patients with similar phenotypes and identifying mutations responsible for clinical pictures, took the inverse diagnostic approach and focused on genotypes.[1] The genome of patients suffering from undiagnosed systemic inflammatory processes and/or recurrent fever was sequenced, and in 25 men a common mutation was detected in codon 41 of the *UBA1* gene on the X chromosome. To date, 3 variants of the mutation have been identified—pMet41Thr, pMet41Val, and pMet41Leu—and although they had initially only been described in men, they have also been detected in women as a consequence of the inactivation of one X chromosome.[3]

Most of the patients in the first series described presented with recurrent fever, cutaneous manifestations, lung involvement, ear or nose polychondritis, and hematological disorders such as macrocytic anemia or myelodysplastic syndromes.[1] Another characteristic of those patients was the presence of vacuoles in erythroid and myeloid

DOI of original article:
https://doi.org/10.1016/j.ad.2022.03.033
* Corresponding author.
E-mail address: miriam.fernandez.parrado@navarra.es (M. Fernández-Parrado).

https://doi.org/10.1016/j.ad.2022.03.038

precursors in bone marrow biopsies. It is likely that in the future new clinical characteristics, such as eye or gastrointestinal involvement, joint pain, or adenopathy will be added to the initial description of phenotypes.[3] The patients in whom the mutation was detected had been diagnosed with, or had met the criteria for, relapsing polychondritis, Sweet syndrome, polyarteritis nodosa (PAN), or giant cell arteritis.

Dermatologic manifestations, which were present in more than 80% of patients, are among the most frequent clinical features and precede systemic symptoms in more than half of the cases.[1,4] Cutaneous manifestations can be similar to those of other known dermatoses, such as Sweet syndrome, and may include pink or violaceous edematous papules on the neck and trunk, erythematous-violaceous plaques and nodules, livedo racemose, or vasculitic lesions similar to those found in PAN.[4] Histopathologically, the skin lesions are characterized by the presence of a dense dermal neutrophilic infiltrate, with variable leukocytoclastic degradation and vessel infiltration, and in some cases, venous thrombosis. The infiltrate consists of neutrophils mixed with precursor myeloid cells positive for CD163 (immature neutrophils and metamyelocytes).[4] In some cases signs of PAN were found in addition to neutrophilic dermatosis.[3,4] Sanger sequencing for *UBA1* in biopsies suggests that the infiltrate is clonal and that the cutaneous manifestations are therefore probably more a consequence of the infiltrate than of an autoinflammatory state.

An algorithm was recently proposed to detect the mutation in patients previously diagnosed with relapsing polychondritis. Given that frequent and diverse cutaneous manifestations are involved in VEXAS syndrome, it would be useful to reach a similar consensus for male patients diagnosed with Sweet syndrome in dermatology departments.[2]

Funding

This work has not received any type of funding.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. N Engl J Med. 2020;383:2628–38.
2. Georgin-Lavialle S, Terrier B, Guedon AF, Heiblig M, Comont T, Lazaro E, et al. Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients. Br J Dermatol. 2022;186:564–74.
3. Zakine E, Schell B, Battistella M, Vignon-Pennamen M-D, Chasset F, Mahévas T, et al. UBA1 variations in neutrophilic dermatosis skin lesions of patients with VEXAS syndrome. JAMA Dermatol. 2021;157:1349–54.
4. Ferrada MA, Sikora KA, Luo Y, Wells KV, Patel B, Groarke EM, et al. Somatic mutations in UBA1 define a distinct subset of relapsing polychondritis patients with VEXAS. Arthritis Rheumatol. 2021;73:1886–95.