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Letter to the Editor

p.(Tyr135His), a new variant associated with familial Mediterranean fever

La p.(Tyr135His), una nueva variante asociada a la fiebre mediterránea familiar

Dear Editor,

Familiar Mediterranean fever (FMF) is the most common inherited autoinflammatory disease.[1] It is transmitted in an autosomal recessive manner, and 393 variants have been identified.

A 51-year-old male, ex-smoker, with depressive anxiety disorder, glaucoma, who had undergone a bilateral phakectomy. He reported suffering from episodes of fever 37 °C–38 °C between the age of 16 and 18 years of periodic onset, and lasting a week. He was under treatment with vortioxetine 20 mg/24 h and anafranil 35 mg/24 h.

He consulted for a control analysis, asymptomatic. In a check of previous routine tests, some showed elevated C-reactive protein, up to 128 mg/l (normal 0–5).

Physical examination revealed only a large, flat, brown, pigmented lesion on the front of the legs and feet (Fig. 1a).

Blood count and biochemistry were normal: beta-2-microglobulin 2.43 mg/l (normal .80–2), complement CH50 > 95U/ml (normal 42–95), tumour necrosis factor (TNF-alpha) 13.1 pg/ml (normal 0–12.4). Angiotensin converting enzyme, interleukin 1, interleukin 6, immunoglobulins, complement C3, complement C4, and vascular endothelial growth factor were normal.

Lupus anticoagulant: 1.32 (positive >1.20). Rheumatoid factor, antinuclear antibodies, ENA SSA/RO, ENA SSB/La, ENA SM, ENA Scl-70, anti-cyclic citrullinated peptide antibody, anti-endothelial cell antibody, anti-proteinase antibody 3, and anti-myeloperoxidase antibody were negative.

Axial tomography of the chest and abdomen showed calcified mediastinal and hilar lymph nodes; a right axillary adenopathy of 10 mm in diameter; bilateral axillary lymph nodes of subcentimetric size, mesenteric, retroperitoneal para-aortic, and bilateral iliac nodes, some of which were calcified; spleen with multiple millimetric calcifications; punctate lithiasis in the middle collecting system of the right kidney and the lower collecting system of the left kidney; a blast lesion was also observed in the right iliac bone.

Skin biopsy of the lesion on the anterior leg showed a hyperpigmented basal layer with atrophy of epidermal papillae; both the papillary and reticular dermis had moderate fibrosis, together with a perivascular lymphocytic inflammatory infiltrate; the subcutaneous adipose tissue at the lobular level had dystrophic, adipocytic, and steatonecrosis changes; the septa were moderately thickened by fibrosis; histiocytes and multinucleated giant cells, both with xanthosis changes, were observed in relation to the areas of lipodystrophy/steatonecrosis, all compatible with lobular panniculitis plus lipophagic histiocytic necrosis (Fig. 1b). Congo red staining of skin, rectal, and subcutaneous fat biopsies was negative.

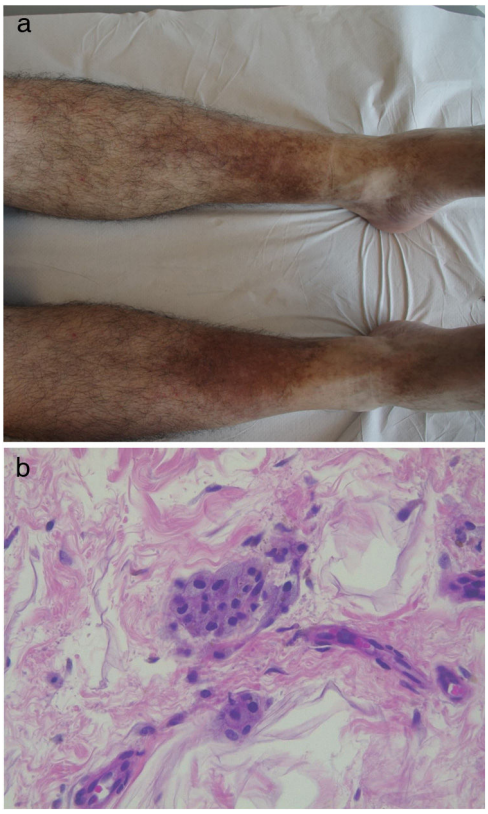

Figure 1. a) Large, flat, large, brown, pigmented lesion on the anterior aspect of the legs and feet. b) Lobular inflammatory infiltrate with histiocytes and multinucleated giant cells, both with xanthosis changes, associated with areas of lipodystrophy/steatonecrosis.

The autoinflammatory disease study detected the heterozygous variant p.(Tyr135His) in the MEFV (Mediterranean fever) gene; this missense-type change predicts the substitution of an amino acid tyrosine for histidine at position 135 of the protein.

FMF is suspected in short, recurrent febrile episodes with asymptomatic intervals, usually occurring before the age of 20 years; erysipeloid lesions on the legs and dorsum of the feet[2] may occur, although rare, and lymphadenopathy may also be observed.[3] Elevations of acute phase reactants are often present during outbreaks.[4] Routine testing showed elevations in CRP, beta-2-microglobulin, and complement CH50, revealing an inflammatory state.

The variant p.(Tyr135His) is not described in clinical databases, nor the scientific literature consulted at the time of writing. It does appear in the dbSNP (database of Single Nucleotide Poly-

morphisms) database (rs145078602), but not in the population frequency database gnomAD (The Genome Aggregation Database). The bioinformatics predictor CADD (Combined Annotation Dependent Depletion) estimates that the change would have a tolerated effect (<10).

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Francisco José Nicolás-Sánchez,[a,*] Lluis Eleuteri Pons i Ferré,[b] Francesc Josep Nicolás-Sarrat,[a] Alberto González Barranquero[c]

[a] *Servicio de Medicina Interna, Hospital Universitari de Santa Maria, Lleida, Spain*
[b] *Eldine Patología, Tarragona, Spain*
[c] *Servei de Cirurgia, Hospital Universitari de Santa Maria, Lleida, Spain*

* Corresponding author.
E-mail address: fnicolas@comll.cat (F.J. Nicolás-Sánchez).

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The Latin-American rheumatology community needs to put the eye on ocular cicatricial pemphigoid

La comunidad reumatológica latinoamericana necesita poner el ojo en el penfigoide cicatricial ocular

Dear Editor,

Mucous membrane pemphigoid is a systemic and scarring autoimmune disease. Isolated ocular involvement has classically been called ocular cicatricial pemphigoid (OCP). This entity can lead to irreversible blindness if not treated early.[1,2] Treatment is always systemic; thereby, ophthalmologists seek the support of rheumatologists, dermatologists, or a clinician with autoimmunity knowledge.[3] Given the lack of epidemiological data in our region, the seriousness of this pathology, and it is supposed unfamiliarity by medical professionals of these specialties, it is proposed to carry out this work. Our objective was to know the familiarity of rheumatologists and ophthalmologists with OCP in our region.

A survey was conducted online through a Google form link. The questionnaire was primarily directed toward rheumatologists and ophthalmologists who are members of scientific societies in America. The questionnaire consisted of 13 questions about the age, sex, country, specialty, principal place of work (public or private institution or private practice), whether or not they are familiar with the entity, how many patients they see annually, the specialties with which they work to address these patients, diagnostic methodology (clinical vs. biopsy), the treatments used, and the difficulties in approaching these patients in daily practice. For those physicians who saw at least two patients with OCP in the last year and answered that they were familiar, we considered them familiar and up-to-date with the disease.

We received 463 surveys, and 433 were included, excluding duplications and those surveyed that did not belong to an American country. Three hundred-seven (70.9%) were rheumatologists, and 112 (25.9%) were ophthalmologists. Other specialties were dermatologists, immunologists, and clinicians. Most participants were from Argentina, Colombia, Chile, and Mexico. Table 1 describes the general characteristics of the respondents.

Forty percent reported being familiar with the OCP. Among them, 66.1% were ophthalmologists and 31.3% were rheumatologists. When we analyzed only the group of ophthalmologists' familiarity with the OCP, we observed that the specialty to which these patients are most referred is rheumatologists (85%).

The main difficulties reported in the management of these patients were: (1) the lack of information, and diffusion of the OCP in the different scientific activities and texts of the specialties involved in treating this entity; (2) the difficulty in accessing and performing the biopsy of the ocular conjunctiva; (3) the difficulties in communication between specialists to carry out an appropriate follow-up.

Like other authors,[2–4] we emphasize the key to success with this entity is to have an early multidisciplinary approach. Considering the main difficulties, we believe that more focus should be placed on increasing the scientific activities related to this disease in congresses and journals, mainly related to rheumatology. Furthermore, it is important to address the challenges associated with biopsies that are likely caused by factors such as the high costs of immunofluorescence, inadequate insurance coverage, and the lack of pathologists specialized in OCP.[4]

A limitation of this study is that the survey distribution may have been different per country. Also, the low number of dermatologists involved maybe was that the survey was primarily driven by the rheumatology field, which may not have effectively reached out to many dermatologists.

Observing the high percentage of unfamiliarity with this entity by rheumatologists (70%) and the significant referral of these patients to rheumatology by ophthalmologists familiar with OCP (85%), it is imperative to work to expand the knowledge, and joint effort between both specialties, to improve and standardize the approach to this entity, which produces irreversible sequelae on the ocular surface.