European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Pyrin-associated autoinflammatory disease with p.Thr577Ala *MEFV* somatic mutation

ARTICLE INFO

Keywords
Mefv
Pyrin-associated autoinflammatory disease
Somatic mutation
Familial mediterranean fever
Colchicine

Dear Editor,

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease worldwide. FMF is classically a recessive disease due to mutations in exon 10 of the *MEFV* gene and affects patients originating from the Mediterranean region. The MEFV gene encode for the protein pyrin, that is involved in the activation of the pyrin inflammasome [1]. The main clinical signs are recurrent inflammatory flares associating fever, abdominal pain, arthralgia and ankle pseudo erysipelas. The most frequent and severe mutation is the p.Met694Val. Colchicine, a pyrin inflammasome inhibitor, is most often effective in preventing attacks and controlling inflammation. Beside this classical presentation, mutation of *MEFV* have been associated with dominant inflammatory diseases such as pyrin associated auto-inflammatory disease with neutrophilic dermatosis (PAAND) [2]. Inflammatory diseases have also been associated with germline mutation at amino-aside position 577 of the *MEFV* gene with different clinical presentation [3,4]. The name Pyrin-associated autoinflammatory disease (PAAD) has been chosen to include all diseases caused by pyrin defects or *MEFV* mutations [5]. Here we report a new form of PAAD associated with a somatic dominant *MEFV* mutation.

A 28-year-old woman of Caucasian French origin through 3 of her grandparents and Algerian, was referred to our consultation for suspected autoinflammatory disease. Theras no other case in her family. She presented since the age of 2 years recurrent episodes associating fever, abdominal pain, erythema of the limbs especially in the ankles (examples provided by the patient are presented in Fig. 1A–C), and arthromyalgia. The febrile episodes lasted 2 to 3 days. The patient displayed a permanent biological inflammatory syndrome which increased in period of febrile crisis with a CRP> 100 mg/L. Digestive endoscopies had shown a pancolitis (Fig. 1D). She displayed neither autoantibodies nor hypogammaglobulinemia. In view of the digestive and articular manifestations, and in the absence of any formal element of classification, she was labelled Crohn-like and spondylarthritis-like. She had received numerous treatments over time, all of which were ineffective: methotrexate, salazopyrin, 3 different anti TNF treatments and ustekinumab. At the time of the consultation, she complained of chronic diarrhea, abdominal pain, knee arthralgia, asthenia, displayed an erythema of the ankle and was inflammatory with CRP=25 mg/L and SAA=26 mg/L. A skin biopsy was performed on the erythematous lesion and showed minimal superficial dermal neutrophilic infiltrate (Fig. 1E). A genetic analysis by next generation sequencing identified the somatic pathogenic variant c.1729A>*G*, p.Thr577Ala in the *MEFV* gene with an allele frequency of 16 % (her parents and son do not carry this mutation). Sanger sequencing results were consistent with a mosaic variant (Fig. 1F). The final clinical diagnosis was thus a Pyrin-associated autoinflammatory disease (PAAD) associated with a dominant variant in *MEFV* exon 8. A functional test of IL1-β release after UCN-01 treatment of patient's monocyte described previously ([6] and supplementary material) confirmed the pathogenic nature of the mutation (Fig. 1G).

She received daily colchicine and anti-IL1 biotherapy with spectacular efficacy. After the disappearance of the diarrhea, the anti-IL1 therapy could be stopped. After 12 months of follow-up, she is perfectly controlled with colchicine alone at 1 mg/d with normalization of CRP (4.3 mg/L) and almost normal SAA (10 mg/L). She had no more fever episodes, and nor more articular symptoms. The abdominal pain and diarrhea resolved under treatment; no follow up endoscopy was performed.

To date, few patients have been described with a dominant form of PAAD related to a missense mutation of *MEFV* at position amino-acid 577 [3,4,7,8], but to our knowledge never in a somatic form. As in the other reported case due to mutations at amino acid position 577 [3,4], the patient had a typical presentation of FMF, except for her ethnic background and the presence of an inflammatory bowel disease (IBD). Interestingly, no patients with IBD have been described [3,4,7,8]. As IBD is not a rare disease, this could be a coincidence. However, the failure of classical IDB treatments and the resolution of IDB after initiation of a pyrin inflammasome inhibitor, i.e. colchicine, are strong arguments that it is related to pyrin inflammasome dysregulation. The spectacular response to colchicine seen in our patient is concordant with the other reported cases [3,4,7,8]. Altogether, the classification of the mutation as "Likely pathogenic" in the Infevers database [9], the presence of other cases with similar presentations, the spectacular colchicine response and the pathogenic functional test of IL1-β release after UCN-01, argue for the pathogenic nature of the mutation and its involvement in the clinical presentation. The relatively low allele frequency is not inconsistent with

https://doi.org/10.1016/j.ejim.2023.11.014
Received 11 September 2023; Received in revised form 5 November 2023; Accepted 8 November 2023

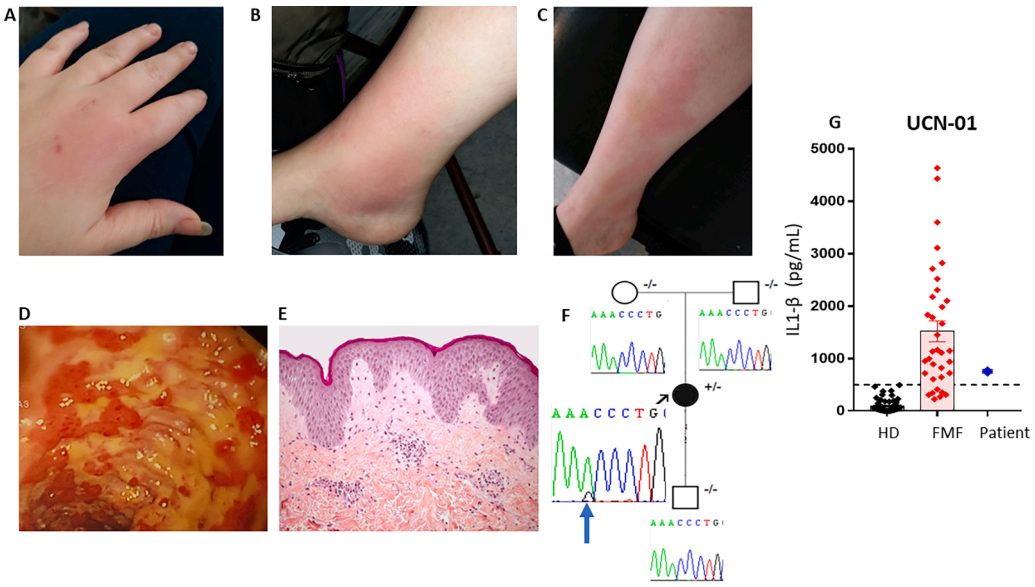

Fig. 1. A-C: Peri articular erythema from the patient. D: Colonoscopy before introduction of colchicine and anti-IL1 therapy of the patient showing diffuse ulceration of the colonic mucosa. E: Skin biopsy performed on the peri-articular erythema of the patient (Hematein, eosin, saffron magnification x200) showing inflammation of the superficial dermis with a slight edema and a scanty, pericapillary and interstitial infiltrate, composed of lymphocytes and neutrophils, without leukocytoclasia or capillary alteration. F: Sanger sequencing chromatogram of the patient and her first degree relatives showing a mosaic *A>G* substitution. Black arrow showing the index case. Blue arrow showing the minor pic corresponding to the G substitution found in deep sequencing. G: IL-1β levels in monocyte supernatants were quantified by ELISA. IL-1β levels secreted by the patient monocytes (blue) were compared to the results obtained from a previously described cohort: HD (healthy donors $n = 64$, black) and FMF patients ($n = 35$, red)[1]. Each dot represents the mean of a triplicate, the bar represents the mean +/- SD of all individuals within one group.

its involvement in the disease, as somatic auto-inflammatory diseases have been described with lower allelic frequencies [10,11]

Amino-acid 577 is located in the central helical scaffold domain. Recently it has been showed that mutations in the central helical scaffold were functionally similar to the B30.2 pathogenic mutations such as p. Met694Val mutations [12]. This demonstration allows us to understand the pathogenic mechanism of mutations at position 577, but it does not explain the dominant character of these mutations.

This case confirms previous publications on the cosmopolitan character of PAAD when the mutation is dominant in position 577. This case illustrates the importance of providing next generation sequencing in patients with severe inflammatory disease, after careful examination of the clinical presentation [13]. Deep-sequencing analysis can detect somatic mutations such as here a mutation affecting 16 % of the cells, whereas Sanger sequencing is less performant for somatic mutations detection. This observation shows the importance of considering monogenic autoinflammatory diseases even in adults.

Declaration of Competing Interest

SGL received Travel grants and honoraria from the SOBI and Novartis laboratories.

Fundings

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Data availability

Data are available on request to the corresponding author.

Acknowledgement

We thank Laurence Pieroni (Unité de Biochimie-Hormonologie, Hospital Tenon, APHP-Sorbonne Université, Paris, France), Philippe Moguelet (Service d'Anatomopathologie, Hospital Tenon, APHP, Paris, France), Lea Savoy (Sorbonne University, AP-HP, Tenon hospital, Department of Internal Medicine, centre de référence des maladies auto-inflammatoires et des amyloses d'origine inflammatoire (CEREMAIA), GRC-28, Paris, France.), Thomas Henry (CIRI, centre International de Recherche en Infectiologie, Univ Lyon, Inserm U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, F-69007, LYON, France), for their help in the care of the patient, for the biological and pathological studies of the case, for their expertise in pyrin-associated autoinflammatory diseases, and for their help with the manuscript.

Authors Contribution

Georgin-Lavialle designed the research study. Alexandre Terré and Sophie Georgin Lavialle performed the final analysis of the data and wrote the manuscript. Sophie Georgin-Lavialle, and Jean-Maxime Piot followed the patient. Guilaine Boursier performed the genetic studies. Flora Magnotti performed the functional test to demonstrate the pathogenicity of the variant. All authors participated to the draft of the paper. All authors approved the final version.

Methods

IL1-β release assay

Monocytes, isolated as previously reported (1), were primed with LPS for 3 h and exposed to UCN-01 (12.5 μM). IL-1β concentration in the supernatant was quantified at 1 h 30 post-addition.

Ethics

The patient agreed that her data were included in the JIR (Juvenile Inflammatory Rheumatism)- cohort; an international multicenter data repository established by the National Commission on Informatics and Liberty (CNIL; authorization number N◦: 914677). She was informed that data collected in medical records might be used for research studies in accordance with privacy rules. She also agreed that her pictures can be used for scientific purpose. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

References

[1] Schnappauf O, Chae JJ, Kastner DL. Aksentijevich I. the pyrin inflammasome in health and disease. Front Immunol 2019;10:1745.
[2] Moghaddas F, Llamas R, De Nardo D, Martinez-Banaclocha H, Martinez-Garcia JJ, Mesa-Del-Castillo P, et al. A novel Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis mutation further defines 14-3-3 binding of pyrin and distinction to Familial Mediterranean Fever. Ann Rheum Dis 2017;76:2085-94.
[3] Stoffels M, Szperl A, Simon A, Netea MG, Plantinga TS, van Deuren M, et al. MEFV mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease. Ann Rheum Dis 2014;73:455-61.
[4] Elhani I, Dumont A, Deshayes S, Georgin-Lavialle S, Giurgea I, Aouba A. Typical Familial Mediterranean Fever associated with the heterozygous missense sequence p.T577N variant of the MEFV gene: report on two Northern European Caucasians relatives in France. Joint Bone Spine 2020;87:251-5.
[5] Boursier G, Hentgen V, Sarrabay G, Koné-Paut I, Touitou I. The changing concepts regarding the mediterranean fever gene: toward a spectrum of pyrin-associated autoinflammatory diseases with variable heredity. J Pediatr 2019;209:12–6. e1.
[6] Magnotti F, Malsot T, Georgin-Lavialle S, Abbas F, Martin A, Belot A, et al. Fast diagnostic test for familial mediterranean fever based on a kinase inhibitor. Ann Rheum Dis 2021;80:128-32.
[7] Endo Y, Koga T, Nakashima M, Mishima H, Yoshiura KI, Kawakami A. Atypical phenotype without fever in a Japanese family with an autosomal dominant transmission of familial Mediterranean fever due to heterozygous MEFV Thr577Asn mutations. Clin Exp Rheumatol 2019;37(Suppl 121):161-2.
[8] Nakaseko H, Iwata N, Izawa K, Shibata H, Yasuoka R, Kohagura T, et al. Expanding clinical spectrum of autosomal dominant pyrin-associated autoinflammatory disorder caused by the heterozygous MEFV p.Thr577Asn variant. Rheumatol Oxf Engl 2019;58:182-4.
[9] Infevers - Tabular list [Internet]. [cited 5 nov 2023]. Available on: https://infevers.umai-montpellier.fr/web/search.php?n=1.
[10] Louvrier C, Assrawi E, El Khouri E, Melki I, Copin B, Bourrat E, et al. NLRP3-associated autoinflammatory diseases: phenotypic and molecular characteristics of germline versus somatic mutations. J Allergy Clin Immunol 2020;145:1254-61.
[11] Kant B, Carbo EC, Kokmeijer I, Oosterman JJM, Frenkel J, Swertz MA, et al. Gene mosaicism screening using single-molecule molecular inversion probes in routine diagnostics for systemic autoinflammatory diseases. J Mol Diagn JMD 2019;21:943-50.
[12] Chirita D, Bronnec P, Magnotti F, Dalmon S, Martin A, Popoff M, et al. Mutations in the B30.2 and the central helical scaffold domains of pyrin differentially affect inflammasome activation. Cell Death Dis 2023;14:213.
[13] Heiser L, Broly M, Rittore C, Touitou I, Georgin-Lavialle S, Boursier G. Predictive clinical and biological criteria for gene panel positivity in suspected inherited autoinflammatory diseases: insights from a Case-Control Study. Genes (Basel) 2023;14:1939.

Alexandre Terré[a], Flora Magnotti[b], Jean-Maxime Piot[c], Guilaine Boursier[d], Sophie Georgin-Lavialle[a,*]

[a] *Sorbonne University, AP-HP, Tenon hospital, Department of Internal Medicine, Centre de référence des maladies auto-inflammatoires et des amyloses d'origine inflammatoire (CEREMAIA), GRC-28, Paris, France*
[b] *CIRI, Centre International de Recherche en Infectiologie, Univ Lyon, Inserm U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, F-69007, LYON, France*
[c] *Service de Rhumatologie, Centre Hospitalier du Mans, le Mans, France*
[d] *Laboratoire de Génétique des Maladies rares et autoinflammatoires, Service de Génétique moléculaire et cytogénomique, CHU Montpellier, Univ Montpellier, CeRéMAIA, Montpellier, France*

[*] Corresponding author at: Department of Internal Medicine, Tenon Hospital, 20, rue de la Chine, Sorbonne University Assistance Publique-Hôpitaux de Paris. centre de référence des maladies auto-inflammatoires et des amyloses inflammatoires (CEREMAIA). 75020 Paris, France.
E-mail address: sophie.georgin-lavialle@aphp.fr (S. Georgin-Lavialle).