In our second case, the marked vascularization present on Doppler led us to consider a differential diagnosis with venous malformations. On ultrasound, venous malformations are seen as tubular structures, occasionally with hyperechoic structures with a posterior shadow (phleboliths), with a venous wave on pulsed Doppler. In this case, as the lesion was small and had not presented episodes of increasing size, we observed a predominance of areas with Doppler flow and a smaller anechoic central region.

In conclusion, Doppler can be a very useful tool for the diagnosis of ADF. The anechoic areas with no flow correspond histologically to the ectatic areas and the regions with Doppler flow correspond to the vascularized and cellular areas.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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# Familial Mediterranean Fever: Diagnostic Difficulties in an Atypical Case☆

## Fiebre mediterránea familiar. Dificultades diagnósticas en un caso atípico

*To the Editor:*

A 68-year-old woman with a history of neurosensorial deafness and anemia of chronic disease consulted for more than 20 years of recurrent episodes of fever, joint and muscle pain, and skin lesions on the arms and trunk. The episodes occurred every 2 to 6 months and lasted around 2 weeks. She was asymptomatic between episodes. Large edematous erythematous plaques arose on her trunk and the root of her upper limbs (Fig. 1), associated with fever of 38 °C. Blood tests were normal. Skin biopsy showed edema and an inflammatory infiltrate of lymphocytes and neutrophils in the superficial dermis, without fibrinoid necrosis (Fig. 2).

She subsequently developed fever associated with erythema and increased temperature in 1 of her legs, with blisters and an abundant exudate (Fig. 3). A gram-negative microorganism was isolated on culture, and this was interpreted as infectious cellulitis. Four months later she presented similar manifestations in her other leg.

Genetic analysis was performed of genes *MEFV*, *TNFRSF1A*, *MVK*, *NLRP3*, *NOD2*, and *PSTPIP1*. The patient was heterozygous for the c.1772T>C variant of gene *MEFV*.

As she also satisfied the Tel-Hashomer diagnostic criteria for familial Mediterranean fever (FMF) (Table 1), she was diagnosed with this entity. Treatment was started with colchicine, which led to a marked improvement in the clinical manifestations.

FMF is the most common autoinflammatory disease of adults.[1] It has a monogenic autosomal recessive inheritance, caused by a mutation in gene *MEFV* (16p13.3), although 20% of patients are heterozygous.[2] This could be because it is actually an autosomal dominant disease with variable penetrance, it was not possible to detect the second mutation due to technical limitations, or that it could be a polygenic disease. Some authors have stated that these patients

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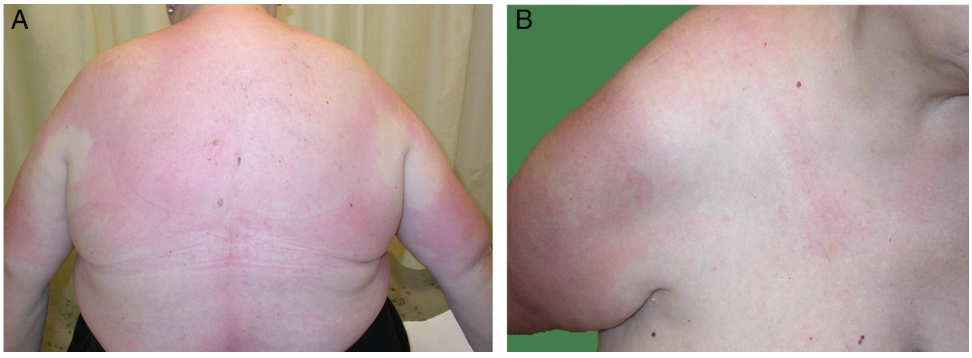


**Figure 1** A and B, Large edematous erythematous plaques with an urticarial appearance and increased local temperature. The lesions were found on the trunk and root of the upper limbs.

have a later onset of the disease, with a shorter duration of outbreaks, milder symptoms, and longer symptom-free intervals.[3]

Gene *MEFV* codes the protein pyrin, also known as marenostrin, which plays a role in regulation of the innate immune response. Alteration of this protein removes control from the pathway, increasing the levels of interleukin 1β, responsible for the inflammatory response in this disease.[4]

Soriano and Manna[5] described 4 clinical phenotypes of the disease:

- *Type 1:* Patients with recurrent episodes of short duration (12-72 h) with fever, acute abdominal pain, joint involvement, acute chest pain due to pleuritis/pericarditis, and various skin manifestations. Patients are usually asymptomatic between outbreaks, although biochemical evidence of the disease can be detected.
- *Type 2:* Patients who develop secondary amyloidosis (AA type) with proteinuria or kidney failure before they develop other signs of FMF, or as the only manifestation in relatives of patients with FMF.
- *Type 3:* Carriers of a mutation of gene *MEFV* with no clinical manifestations of the disease and no amyloidosis. This occurs in endemic populations (such as Iraqi Jews and Ashkenazi Jews), with a prevalence of 1 in 25 to 1 in 300 persons. Although the majority never present clinical manifestations, some do develop amyloidosis with time (phenotype 2).
- *FMF-like:* Heterozygous patients with mild clinical manifestations of the disease. Our patient falls into this phenotype.

Cutaneous manifestations of the disease occur in 10% to 40% of affected patients.[6] Only erysipelas- or cellulitis-like lesions, seen in 5% to 30% of patients with FMF, are considered specific, and they arise on the anterior surface of the legs and dorsum of the feet. Histology reveals a perivascular dermal infiltrate made up mainly of mononuclear cells and neutrophils, but with no vasculitis.[7] The episodes that affected our patient's legs probably corresponded to this clinical presentation. Panniculitis can present as erythema nodosum or neutrophilic pan-

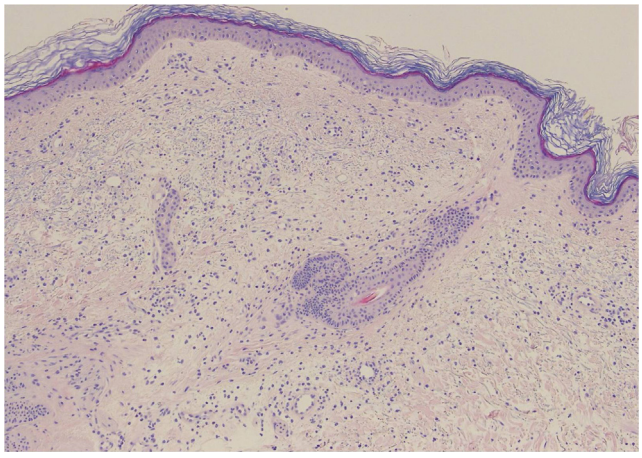

**Figure 2** Edema associated with a moderate inflammatory infiltrate of lymphocytes and neutrophils in the superficial dermis, with occasional images of leukocytoclasia. No extravasation of red blood cells is observed, nor the presence of hemosiderophages or lesions of fibrinoid necrosis in the vessel walls. Hematoxylin and eosin, original magnification ×20.

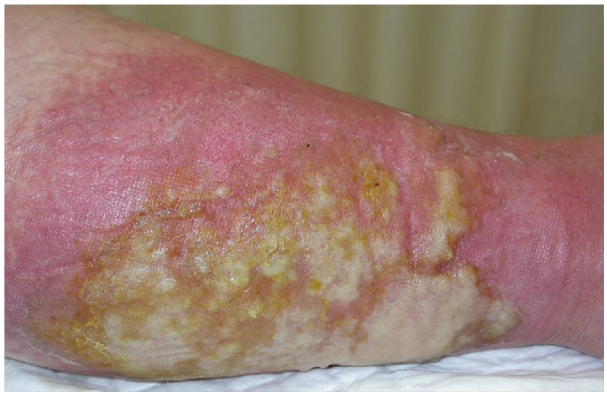

**Figure 3** Hot erythematous plaque on a leg, with blister formation and an abundant exudate.