Neutrophilic Lobular Panniculitis as an Expression of a Widened Spectrum of Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is considered to be an autosomal recessive disease, though it is controversial. The marenostrin-encoding fever gene (MEFV) is responsible for FMF. The most frequent mutation is M694V, which represents a genetic risk factor for development of amyloidosis and more severe disease. The classic clinical picture consists of generally short recurrent febrile episodes, serositis, and erysipelas-like erythema (ELE). Colchicine is the treatment of choice for prevention of the attacks and AA amyloidosis.

With isolation of the MEFV gene in 1997, incomplete or “atypical” forms of FMF have been reported and are considered by some authors an expanded spectrum of the disease.

Report of a Case | An infant without relevant medical or family history presented with tender, erythematous, contusiform, warm nodules of irregular shape on the limbs (Figure 1) and face. The lesions healed as grayish macules without lipoatrophy. Coinciding with the skin lesions, she had periodic febrile episodes (temperature up to 40°C) lasting from 3 days to several weeks, malaise, and increased levels of acute-phase reactants. No other signs or symptoms were observed.

Three skin biopsy specimens were obtained. Histologic examination revealed a predominantly lobular neutrophilic panniculitis without evidence of necrosis, vasculitis, crystals, destruction of adipocytes, or infiltration at eccrine structures. Periodic acid–Schiff, Grocott, and EBER stainings were negative. Lipophasic histiocytes and giant cells were present in older lesions (Figure 2). Our differential diagnosis included pancreatic panniculitis, α1-antitrypsin deficiency, infective panniculitis, and panniculitis associated with rheumatic disease. We also considered subcutaneous Sweet syndrome, idiopathic infantile febrile panniculitis, and autoimmune inflammatory disease.

The patient’s clinical course was complicated, with over a year of recurrent episodes, malaise, corticosteroid dependence, and no response to methotrexate, 2.5 mg/wk, or non-steroidal anti-inflammatory drugs. All laboratory findings were negative but for the genetic evaluation for autoimmune inflammatory syndromes that evidenced an M694V single mutation in the MEFV gene. Colchicine treatment was started at 0.5 mg/d. After 2 weeks of treatment, the patient did not present new episodes. This response persisted after 13 months of treatment. The patient satisfied major and minor Tel Hashomer criteria corresponding to a “probable” diagnosis.

Discussion | In the multiple articles that describe clinical and genetic features of FMF, 10% to 40% heterozygous mutations were detected. In fact, there is a series of 94 patients carrying a single mutated allele and sharing clinical features with our case: a younger age of onset, longer febrile periods, and a majority of skin eruptions that were not typical ELE. The experts highlight the clinical and therapeutic importance of these single mutations and propose a therapeutic trial with colchicine to support FMF diagnosis. Finally, some authors warn about an expanded spectrum of FMF with new recurrent clinical manifestations that should be considered in cases with rare mutations and mutations in heterozygosis.

The genetic explanation for developing symptoms while carrying a single mutated allele lies in several hypotheses: a dominant inheritance with incomplete penetration under certain environmental backgrounds, oligogenism, difficulties in the detection of rare mutations, and pseudodominance phenomenon.
Lobular neutrophilic panniculitis has been reported in 3 adult patients with FMF.\(^4\)\(^-\)\(^6\) In all cases, there was a long personal history of FMF with serositis and periodic fever. Two of them had typical ELE and were undergoing hemodialysis. However, in our patient, panniculitis was the main clinical manifestation along with periodic fever. We report a case encompassed in the clinical spectrum of FMF. To our knowledge, this is the first observation of lobular panniculitis as the main clinical expression of FMF. Some patients misdiagnosed as having idiopathic infantile febrile panniculitis could be included in the spectrum of FMF and might benefit from a correct diagnosis and treatment preventing a complication as severe as AA amyloidosis.

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Conflict of Interest Disclosures: None reported.