Colchicine-responsive chronic recurrent multifocal osteomyelitis with MEFV mutations: A variant of familial Mediterranean fever?

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Colchicine responsive chronic recurrent multifocal osteomyelitis with *MEFV* mutations: A variant of familial Mediterranean fever?

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Short title: Colchicine responsive chronic recurrent multifocal osteomyelitis with *MEFV* mutations

Key message: The MEFV gene might be associated with more than typical FMF.

Sir, Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by self-limited recurrent attacks of fever with serositis such as peritonitis, pleuritis and arthritis [1]. FMF is caused by mutations in *MEFV* gene [2]. This gene had been considered to be responsible only for FMF in the past, however, recent reports show that *MEFV* gene is associated with more than typical FMF and is linked to additional clinical presentations within the family of the autoinflammatory diseases [2-4]. Here, we describe a case of colchicine responsive chronic recurrent multifocal osteomyelitis (CRMO) with *MEFV* gene mutations.

A 14-year-old female was referred with fever of unknown origin persisting for 15 days. Physical examination was unremarkable. Laboratory findings showed normal white blood cell count (3.9 $\times 10^9$/L), high levels of CRP (3.1mg/dl), accelerated erythrocyte sedimentation rate (72mm/h), normal levels of immunoglobulins and negative autoantibodies. Blood culture was negative. Unexpectedly, gallium (Ga) scintigraphy on day 3 after admission demonstrated significant uptake in bilateral proximal region of tibia (Figure A). Plain radiography showed no significant findings (Figure D) but magnetic resonance imaging (MRI) demonstrated multifocal lesions whose intensity was low in T1 weighted condition, high in T2 weighted condition in bilateral tibia (Figure E). The biopsy of left tibia showed non-specific inflammatory changes and no

malignant cells. The culture of bone marrow was negative. She had severe pain of left heel on day 21. MRI on day 23 demonstrated multifocal lesions whose intensity was low in T1 weighted condition, high in T2 weighted condition in bilateral tarsal bones (Figure F). Ga scintigraphy on day 38 demonstrated significant uptake in left calcaneus and bilateral femur (Figure B). From these findings, the diagnosis of multifocal recurrent osteomyelitis was made. No evidence of bone destruction or hyperostosis was observed at the time of diagnosis. High fever continued despite the treatment with appropriate antibiotics and naproxen for 8 weeks. However, she was relieved dramatically from high fever soon after colchicine (2mg/day) was started. The mutation analysis demonstrated the heterozygous mutation of E148Q-P369S-R408Q in *cis* on one allele of *MEFV* gene. But no mutation wad found in *LPIN2* gene. Colchicine dose was gradually decreased to 0.5mg/day and daily colchicine therapy (0.5mg/day) relieved her from febrile attacks for 1 year, although she had one episode of osteomyelitis in left fibula (Figure C) when the patient ceased to take colchicine.

FMF is an autosomal recessive, inherited periodic inflammatory syndrome, characterized by self-limited recurrent attacks of fever with serositis such as peritonitis, pleuritis and arthritis [1]. The disease is common among people coming from eastern Mediterranean ancestry. The mainstay of treatment is cochicine which is effective for

both relieving symptoms and preventing secondary amyloidosis. *MEFV* gene encodes a protein named pyrin, which is expressed in neutrophils and monocytes. The function of pyrin is still unknown and remains to be determined.

MEFV gene had been considered to be responsible only for FMF in the past. However, about one-third of patients with FMF have a single mutation on one allele. This finding suggests that FMF might be transferred as an autosomal dominant trait with partial penetration. Another possibility is that an additional, unidentified gene might be associated with the disease in these patients with single allele mutation.

Recently it has been reported a case with heterozygous *MEFV* mutations and distinct clinical presentations not typical for FMF, colchicine responsive recurrent episodes of muscle pains [3]. These reports including our case show *MEFV* gene is associated with more than a single disease (FMF) and is linked to additional clinical presentations within the family of the autoinflammatory diseases [4,5] and some rheumatic diseases such as s-JIA [6,7].

The mutation analysis in our patient demonstrated the heterozygous mutation of E148Q-P369S-R408Q. In the whole list of 186 sequence alterations reported in Infevers - an online database for autoinflammatory mutations available at http://fmf.igh.cnrs.fr/ISSAID/infevers [8], this mutation is reported to be associated with

atypical clinical presentations for FMF.

CRMO is an ill-defined inflammatory disease. In typical cases, multiple bone lesions with apparent bone destruction, hyperostosis and pustulosis of the skin are seen [9]. But there are variable clinical manifestations, which make differential diagnosis of CRMO often difficult. LPIN2 mutation is detectable in a syndrome form of CRMO known as Majeed syndrome [10], but for most cases responsible gene is unknown.

CRMO is unusual, or unexpected manifestation for FMF, and this is the first case of CRMO with *MEFV* mutations to our knowledge. To start the treatment with colchicines promptly, thereby relieving symptoms and preventing secondary amyloidosis, the mutation analysis of *MEFV* gene should be performed in cases of CRMO.

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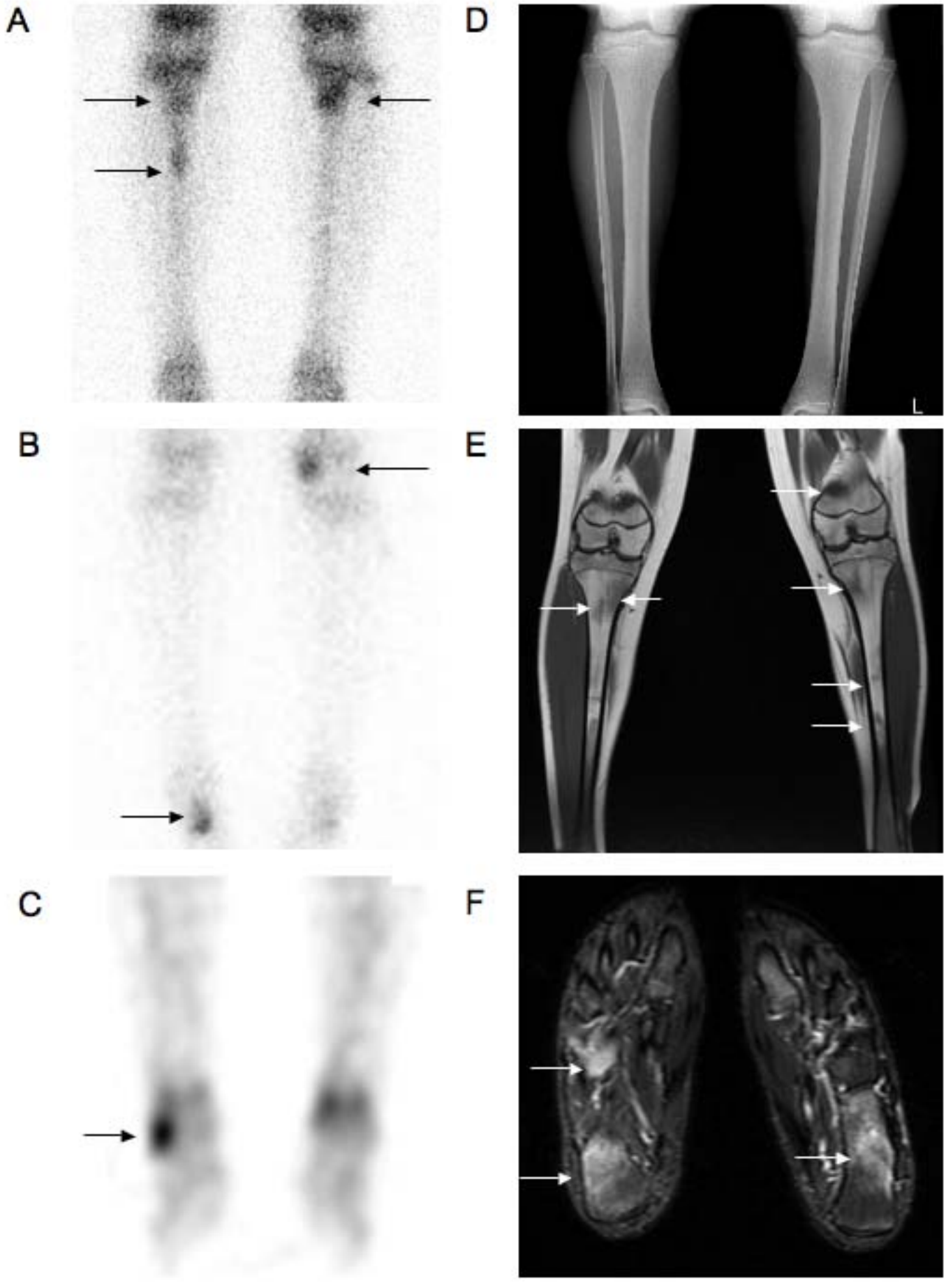
Figure legends

A-C: Gallium scintigraphy: the image on day3 (A) showing significant uptake in bilateral proximal region of tibia. day38 (B) showing significant uptake in left calcaneus and bilateral femur. 9 months later (C) showing significant uptake in left fibula. D: A plain X-ray, frontal view, showed no significant findings including screlosis in bilateral tibia. E, F: Magnetic resonance imaging: the T1-weighted image on day3 (E) showing multiple lesions whose intensity was low in bilateral tibia. The T2-weighted image on day 23 (F) showing multiple lesions whose intensity was high in bilateral tarsal bones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