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Case Report

Improvement of Liver Involvement in Familial Mediterranean Fever After the Introduction of Canakinumab: A Case Report

Maria Grazia Massaro[1], Maurizio Pompili[1,4], Luca L. Sicignano[1], Fabrizio Pizzolante[1], Elena Verrecchia[1], Fabio M. Vecchio[3,4], Donato Rigante[2,4] and Raffaele Manna[1,4*].

[1] Division of Internal Medicine, Rare Diseases and Periodic Fevers Research Centre, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy.
[2] Department of Life Sciences and Public Health, Rare Diseases and Periodic Fevers Research Centre, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy.
[3] Department of Pathology, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy.
[4] Università Cattolica del Sacro Cuore, Rome, Italy.

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Abstract. Hepatic involvement in familial Mediterranean fever (FMF) ranges from a nonspecific increase in liver enzymes to cryptogenic cirrhosis, and the liver is mostly involved in patients bearing the M694V *MEFV* mutation in homozygosis. A 44-year-old Jewish woman with FMF developed nonalcoholic steatohepatitis during colchicine treatment (2,5 mg per day), confirmed by both elastography and liver biopsy. Therefore, combined therapy with the interleukin-1 (IL-1) blocking agent canakinumab (150 mg every four weeks) and colchicine (at a reduced dose of 1.5 mg per day) was started. Three months later, transaminases became normal, and after further six months, there was a marked improvement of liver fibrosis. IL-1 blockade has the power to halt or mitigate liver involvement in FMF patients. However, further experience is required to assess its therapeutic potential in the most severe patients with the hepatic disease who are partially responsive to long-term prophylaxis with colchicine.

Keywords: Familial Mediterranean fever; Autoinflammation; Periodic fever; Steatosis; Hepatitis; Colchicine; Interleukin-1; Innovative biotechnologies; Anakinra; Canakinumab; Personalized medicine.

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Correspondence to: Raffaele Manna, MD, PhD. Institute of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica Sacro Cuore, Rome, Largo A. Gemelli 8, 00168 Rome, Italy. Tel: +39 06 30159433. Fax: +39 06 35502775. E-mail: raffaele.manna@policlinicogemelli.it

Introduction. Familial Mediterranean fever (FMF) is the oldest and most frequent of all known hereditary periodic fever syndromes:[1] its febrile attacks (with peaks over 39-40°C) have a length of about 1-3 days and are characterized by self-limited serositis, joint inflammation and skin manifestations such as erysipelas-like erythema.[2-8] Recurrent polyserositis may be a strongly suggestive clue to diagnose FMF.[9,10] Secondary renal amyloidosis represents the most ominous complication of FMF, usually found in 8.6% of cases according to a multicenter study performed in Turkey.[11] Liver was not considered a district typically involved in FMF, except for liver amyloidosis, which might occur and display an aggressive course.[12] To date, FMF has been linked to a spectrum of liver manifestations ranging from a mild-to-moderate increase of liver enzymes to cryptogenic cirrhosis.[13] Colchicine is the mainstay of FMF treatment since

1972,[14,15] and its efficacy has been largely proved.[16] Despite the maximum tolerated colchicine dose, 5-10% of FMF patients experience more than one attack monthly[17,18] and are defined as colchicine non-responders. Interleukin-1 (IL-1) blockade is considered the gold-standard treatment in refractory FMF, with several reports having demonstrated both efficacy and safety of anakinra and canakinumab.[19-22]

We report a young woman with FMF, undergoing colchicine therapy since the age of 3, who had a frank liver involvement at both laboratory and histological assessment, who progressively improved along with anti-IL-1 treatment.

Case Report. A 44-year-old Jewish woman was diagnosed to have FMF at the age of 3 years due to recurrent febrile episodes (until 40°C) lasting less than 48 hours and occurring three times/monthly combined with recurrent erysipelas-like erythema on the legs, pericardial effusion, recurrent abdominal pain, and arthromyalgia. The diagnosis was confirmed at a genetic level, finding the M694V mutation (in homozygosis) in the *MEFV* gene. Colchicine was started and gradually increased during early adulthood, up to an effective dose of 2.5 mg/day, begun at 29 years, and successfully continued non-stop with good tolerance. The patient had endometriosis at the age of 25 so that she underwent laparoscopy with adhesiolysis and removal of multiple endometriotic foci in the peritoneum, uterus, and annexes. Her more recent medical history was also characterized by insulin resistance and mixed anxiety-depressive disorder. For these reasons, she received estrogen-progestin therapy for about ten years and metformin combined with anti-depressive drugs (venlafaxine, reboxetine) plus benzodiazepines for about three years.

In 2018, after colchicine use for almost 40 years and 15 years after the last increase of colchicine dose (to 2,5 mg/die), the serum level of both transaminases was found abnormal: alanine aminotransferase was repeatedly over 140 IU/l and aspartate aminotransferase over 90 IU/l. The general activity of FMF seemed relatively controlled, as serum amyloid-A (SAA) was 0.74 (n.v. <0.5). Transaminases had been previously within normal limits at the previous patient's follow-up evaluations, and no changes were noted due to therapies taken by the patient. No viral infections could be detected (serology for hepatitis A-B-C, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus was negative). The patient also denied taking toxic substances, such as alcohol or illicit drugs. The autoimmunity panel was completely negative (except for a slight positivity of anti-nuclear antibodies, 1:160). No worsening of FMF typical symptoms was observed during this period.

The increased level of transaminases was also confirmed by many tests performed with monthly frequency. Liver ultrasound assessment revealed standard dimensions, but inhomogeneous echo-structure as well as moderate steatosis. Neither focal lesions nor intrahepatic biliary tract abnormalities were documented. Furthermore, a liver elastography study carried out utilizing a dedicated convex probe through the "point shear wave" technique (Esaote9 XP) with multiple sampling (10 areas) on the right lobe revealed an increased index of elasticity equal to 10.5 kPa. Given the persistently high transaminases, the patient underwent liver biopsy. Histology showed mild steatosis with widespread hydropic degeneration of hepatocytes and centrilobular balloniform activation of CD68+ Kupffer cells, containing PAS-positive material. This morphological report was compatible with steatohepatitis (**Figure 1**). However, these results were not consistent with colchicine-induced liver injury, which occurs in cases of drug overdose, characterized by typical histopathological elements, i.e., anisonucleosis with enlarged nuclei, multiple nucleoli and frequent mitotic figures arrested in metaphase[23], which were not present.

Despite the increase of transaminases, it was not possible to reduce colchicine dose alone, as the same patient had presented different disease relapses if colchicine was reduced to 2 mg/day. For this reason, we decided to start a combined therapy with canakinumab (150 mg every four weeks) and piecemeal reduced dose of colchicine (until 1.5 mg/day). Three months after starting canakinumab, there was a substantial reduction in the transaminases next to normalization. In addition, liver elastography performed six months from initiating canakinumab revealed a sound improvement in the steatosis framework (6.1 kPa *versus* 10.5 kPa).

To date, the patient is still receiving the same therapy based on canakinumab (150 mg every four weeks) and colchicine (1.5 mg/daily), while transaminases have remained in the standard range. There was no exacerbation of FMF typical manifestations, and the disease is currently in remission.

Discussion. FMF is an autoinflammatory disease characterized by recurrent self-limiting episodes of fever and polyserositis.[1,5-7,10] It is the best-known and most common monogenic fever syndrome, which shows a preferential ethnic distribution in Turks, Armenians, Jews, and Arabs.[10,24] This autosomal recessive pathology is caused by mutations in the *MEFV* gene, which encodes for pyrin. Pyrin has a relevant role in controlling the innate immune system and inflammation activation: its functional abnormality causes aberrant activation of the inflammasome with overproduction of proinflammatory cytokines, in particular IL-1.[25] Clinically, the disease is characterized by recurrent inflammation in the serosal membranes, joints, and skin with long-term complications such as renal amyloidosis, which might lead to renal failure, if overlooked.[26]

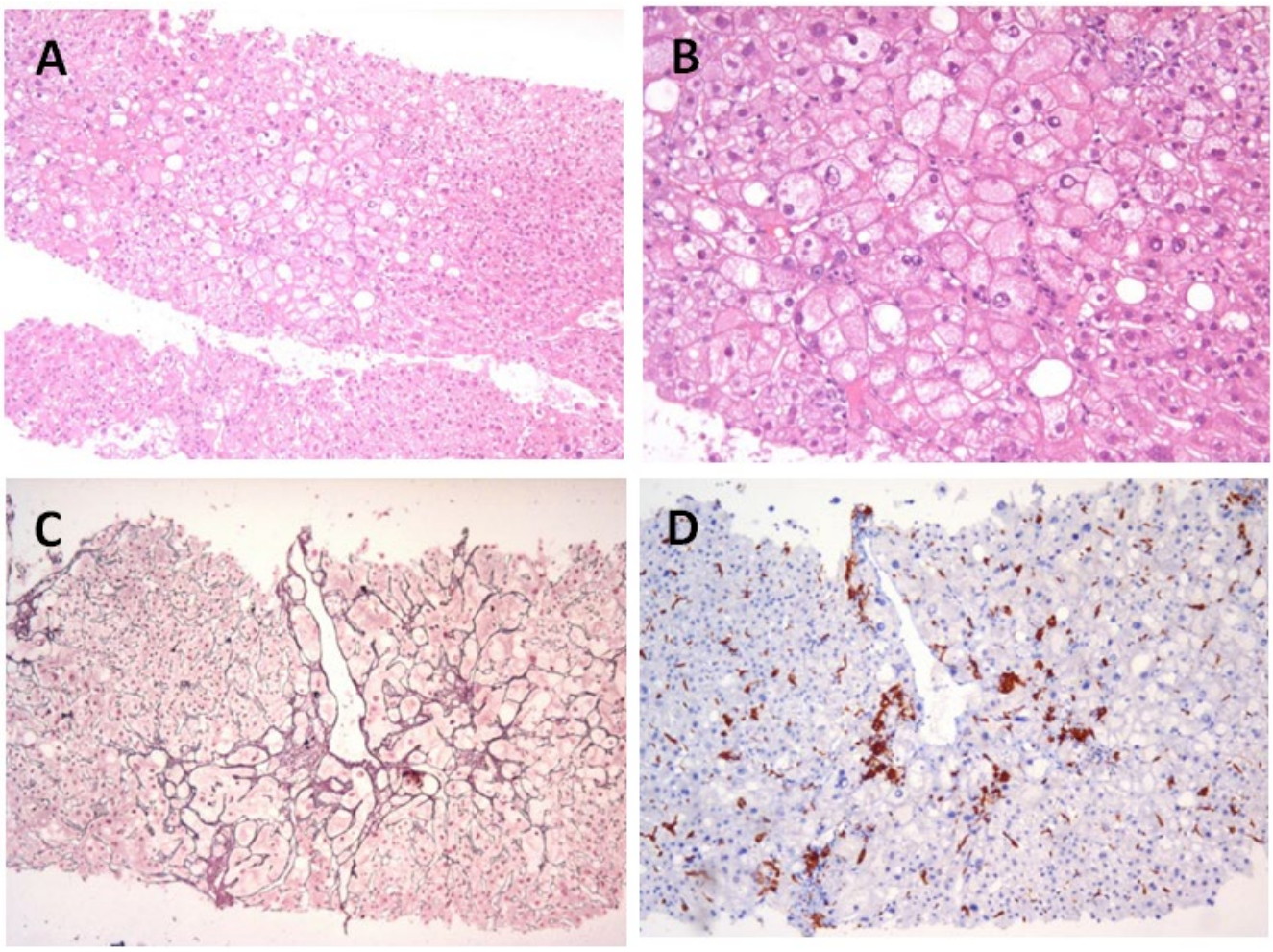

Figure 1. Liver biopsy showing mild steatosis with ballooning cells and some glycogenated nuclei **(A, B)**. In the centrilobular zone, the reticulum stain highlights fibrosis (**C**). Numerous CD68+ and PAS/diastase+ macrophages are also present (**D**).

Untreated FMF is associated with ongoing persistent inflammation and subsequent accumulation of SAA in different target-organs such as kidney, but also liver.[1,5-7,10,27,28] For a long time, the liver was not considered typically involved in FMF, and AA amyloidosis was considered the only possible culprit in the case of hepatic involvement.[12] However, an increase of liver enzymes does not occur in the case of amyloidosis,[13] as the most frequent signs of liver AA amyloidosis are an increased level of alkaline phosphatase and hepatomegaly.[29]

To date, liver involvement in FMF has been widely recognized and reported: both types of *MEFV* mutation and overproduction of IL-1 are probably involved in the damage progression.[30,31] Experiments in mice have shown that an abundant release of IL-1 causes inflammation, pyroptosis, and collagen deposition in the liver with subsequent increase of liver enzymes.[13,32] Two conflicting studies have enhanced our knowledge about the connection between FMF and liver involvement, and more between FMF and nonalcoholic fatty liver disease (NAFLD). The survey conducted by Rimar et al. enrolled 27 patients with FMF but without a frank metabolic syndrome and found that 75% of patients had NAFLD. The conclusion of this study hypothesized a correlation between FMF and NAFLD.[33] Conversely, the survey conducted by Sarkis et al., which enrolled 52 patients with FMF and 30 healthy controls, showed similar rates of NAFLD in the FMF population compared to the healthy one.[34] Indeed, in the study by Rimar et al., FMF patients had fewer risk factors for NAFLD, and NAFLD was demonstrated by biopsy, which is more sensitive than ultrasound.[35] A different study conducted by Tweezer-Zaks et al. documented that M694V homozygosity was relatively more frequent among FMF patients with NAFLD and nonalcoholic steatohepatitis.[36]

From a therapeutic point of view, colchicine is the first-choice option for FMF management since 1972.[14,15,37] The exact mechanism of action underlying colchicine efficacy is not entirely understood: current evidence suggests that colchicine downregulates multiple inflammatory pathways and modulates innate immunity.[38] Colchicine has a narrow therapeutic range, and hepatotoxicity as a possible consequence of long-term administration has been shown.[23] In fact, colchicine intoxication with daily doses higher than 5 mg might determine liver toxicity.[13,38] Of note, the usual doses used to prevent FMF attacks do not seem to bring about a significant increase in liver enzymes in most

cases.[40] A potentially life-threatening complication of some autoinflammatory disorders like FMF may be macrophage activation syndrome, characterized by increased hemophagocytic activity in both bone marrow and liver, combined with fever and different signs of liver damage.[41,42] Furthermore, various scores have been created to quantify organ damage (including liver) or compare disease outcome in patients with autoinflammatory disorders,[43-45] and some of these have been created explicitly for FMF.[46]

Different drugs can come to the rescue for FMF patients who are colchicine-intolerant and non-responders or for those displaying adverse effects to colchicine. Both anakinra, the IL-1 receptor antagonist given subcutaneously daily, and canakinumab, the long-acting specific monoclonal antibody against IL-1β canakinumab, given subcutaneously every four weeks, can be extremely active in the management of another autoinflammatory disorder, which is the cryopyrin-associated periodic syndrome, almost fully mediated by IL-1.[47] As an inappropriate production of IL-1 also plays a central role in the pathogenesis of FMF attacks, blocking IL-1 by specific biological anti-IL-1 drugs should be an ideal strategy in colchicine-resistant patients with FMF.[48,49] Anakinra and canakinumab have been used in the most difficult-to-treat patients with FMF, though recently it has emerged that canakinumab is better-tolerated for less frequent injection-site reactions.[50] It is remarkable that in our patient canakinumab combined with colchicine (at a reduced dose) resulted in normalization of transaminases, in the reduction of fibrosis markers and in a definite improvement of liver steatosis.

Conclusions. Clinical studies are needed to confirm the efficacy of anti-IL-1 drugs such as canakinumab in inducing the regression of liver involvement in FMF patients. If so, this drug might represent an excellent therapeutic alternative for all FMF patients with evidence of hepatic disease. Given the pathogenetic mechanism, underlying liver involvement in FMF, and considering the mode of action of anti-IL-1 treatments, a protective effect of IL-1 blockade for the development of liver complications is conceivable.

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