Letters to the Editors

Late-onset protracted febrile myalgia syndrome successfully treated with colchicine owing to heterozygous *MEFV* exon 2 variants

Sirs,

Protracted febrile myalgia syndrome (PFMS) is a rare form of familial Mediterranean fever (FMF) characterised by prolonged severe myalgia with high levels of C-reactive protein and serum amyloid A, which sometimes develops with fever, abdominal pain and arthritis associated with FMF. We report a rare case of a Japanese PFMS patient with late disease onset and a good response to colchicine owing to multiple heterogynous *MEFV* exon 2 variants.

A 52-year-old Japanese woman with no family history of autoinflammatory diseases experienced recurrent attacks of exercise-induced severe myalgia in the proximal limbs, lasting for 1–4 weeks every 3 months since the age of 45 years. The attacks were sometimes followed by high fever for the first 1–3 days. She visited an orthopaedic surgeon, and her condition was slightly relieved by treatment with non-steroidal anti-inflammatory drugs (NSAIDs) after every attack. In February 2018, she again experienced prolonged myalgia and was admitted to our department. Laboratory findings during the attack showed normal creatine kinase and aldolase levels and high C-reactive protein levels (6.7 mg/dL). Immunological and serological results and infection-associated assays were all negative. A thoracic-abdominal computed tomography scan revealed no abnormalities. Bilateral thigh magnetic resonance imaging revealed a swelling with increased signal intensity in the left biceps femoris muscle. Her symptoms gradually disappeared in 4 weeks with rest and treatment with NSAIDs. Genetic analyses for *MEFV* and TNFAIP3 through direct sequencing revealed heterozygous L110P, E148Q and G304R variants in exon 2 of *MEFV*. In May 2018, she experienced myalgia with high fever and was administered 1.0 mg/day of colchicine, following which her symptoms gradually disappeared in 7 days; she was eventually diagnosed with PFMS. Since then, she has never experienced attacks and her remission has been maintained for 12 months with continuous colchicine therapy. Our patient had heterozygous L110P, E148Q and G304R variants in *MEFV* exon 2. Although most previous reports have shown patients with PFMS to harbour heterozygous or homozygous M694V mutations (1, 2), few cases of PFMS associated with homozygous E148Q mutations have been reported (3, 4). To our knowledge, this is the first report of a patient with PFMS associated with multiple heterogynous *MEFV* exon 2 variants.

Late-onset FMF (LOFMF), defined as FMF onset at >40 years of age (5), is rare (6). Consistent with the features of FMF, most patients with PFMS exhibit early disease onset (2, 7); thus, our case with late-onset PFMS is very rare. The genetic characteristics of patients having FMF in Japan include a lower percentage of *MEFV* exon 10 mutations with high penetrance and a higher percentage of *MEFV* exon 2 mutations with low penetrance compared with patients having FMF in Western countries (8). Our previous study indicated that LOFMF patients have a lower percentage of *MEFV* exon 10 mutations, which contributes to these patients being more common in Japan than in Western countries (8). Therefore, it is important to recognise that PFMS, particularly later onset PFMS, may be associated with heterogynous *MEFV* exon 2 variants, even in a country with patients having a lower percentage of *MEFV* exon 10 mutations.

Prolonged myalgia associated with PFMS is generally resistant to colchicine and shows a good response to corticosteroids. As FMF owing to *MEFV* exon 2 variants contribute to milder phenotype and better response to colchicine (9), our findings suggest that PFMS owing to *MEFV* exon 2 variants also might show a good response to colchicine. In addition, other hereditary autoinflammatory diseases-related genes variants may influence severity or response to colchicine in patients with PMFS, and thus it is required to prospectively investigate those variants among them.

Y. ENDO, *MD*
T. KOGA, *MD, PhD*
K. FURUKAWA, *PhD*
R. SUMIYOSHI, *MD*
K. ICHINOSE, *MD, PhD*
A. KAWAKAMI, *MD, PhD*

Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Medical Sciences, Japan.

Please address correspondence to:
Dr Tomohiro Koga,
Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Medical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
E-mail: tkoga@nagasaki-u.ac.jp

Competing interests: none declared.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2019.

References

1. BRIK R, SHINAWI M, KASINETZ L, GERSHONI-BARUCH R: The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease. *Arthritis Rheum* 2001; 44: 1416-19.
2. SIDI G, SHINAR Y, LIVNEH A, LANGEVITZ P, PRAS M, PRAS E: Protracted febrile myalgia of familial Mediterranean fever. Mutation analysis and clinical correlations. *Scand J Rheumatol* 2000; 29: 174-76.
3. SOYLU A, KASAP B, TURKMEN M, ULGENALP A, UZUNER N, KAVUKCU S: Protracted febrile myalgia syndrome in a patient with familial Mediterranean fever homozygous for the E148Q mutation. *Semin Arthritis Rheum* 2008; 38: 161-62.
4. FUJIKAWA K, MIGITA K, TSUKADA T, KAWAKAMI A, EGUCHI K: Protracted febrile myalgia syndrome in a Japanese patient with fasciitis detected on MRI. *Intern Med* 2014; 53: 2817-9.
5. TAMIR N, LANGEVITZ P, ZEMER D *et al*.: Late-onset familial Mediterranean fever (FMF): a subset with distinct clinical, demographic, and molecular genetic characteristics. *Am J Med Genet* 1999; 87: 30-35.
6. SOHAR E, GAFNI J, PRAS M, HELLER H: Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967; 43: 227-53.
7. LANGEVITZ P, ZEMER D, LIVNEH A, SHEMER J, PRAS M: Protracted febrile myalgia in patients with familial Mediterranean fever. *J Rheumatol* 1994; 21: 1708-9.
8. ENDO Y, KOGA T, ISHIDA M *et al*.: Musculoskeletal manifestations occur predominantly in patients with later-onset familial Mediterranean fever: Data from a multicenter, prospective national cohort study in Japan. *Arthritis Res Ther* 2018; 20: 257.
9. TOPALOGLU R, BATU ED, YILDIZ C *et al*.: Familial Mediterranean fever patients homozygous for E148Q variant may have milder disease. *Int J Rheum Dis* 2018; 21: 1857-62.