CASE REPORT

A Case Report of Familial Mediterranean Fever Diagnosed Following the Total Knee Arthroplasty

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Introduction

Postoperative fever following orthopedic surgical procedures is common, but the cause of fever and its relation to infections is often unclear. Periprosthetic joint infection is a devastating complication following the total joint arthroplasty [8]. In the USA, periprosthetic joint infection is currently the most common indication for revision total knee arthroplasty and the third most common indication for revision total hip arthroplasty [2, 8]. Since no highly accurate diagnostic method exists, the diagnosis of infection is based on a combination of clinical suspicion, serological

tests, culture results, histology, and basic molecular techniques.

We present the case of a 62-year-old female who presented to our clinic with a fever of unknown origin following a total knee replacement. She was suspected to have a periprosthetic joint infection. Because of her recurrent febrile episodes associated with peritonitis, pleuritis, and synovitis, familial mediterranean fever (FMF) was suspected based on the Tel-Hashomer criteria, if two major or one major + two minor criteria are met (Major criteria are (1) recurrent febrile episodes associated with peritonitis, pleuritis, or synovitis; (2) amyloidosis of AA-type without a predisposing disease; and (3) favorable response to daily colchicine. Minor criteria are (1) recurrent febrile episodes, (2) erysipelas-like erythema, and (3) positive history of familial mediterranean fever in a first degree relative) [5]. As part of the workup for her fever, a genomic search for the mediterranean fever gene (MEFV) was performed, and heterozygous L110P, E148Q, and M694I mutations were found in the patient. FMF was confirmed by the mutation in the hot spot of *MEFV*. The patient's symptoms were successfully controlled by administration of colchicine.

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Case Report

A 62-year-old female patient complaining of a bilateral knee pain for 2 years presented to our outpatient clinic in December 2007. She had been prescribed with oral prednisolone (5 mg/day) for 8 years by her primary physician because of a suspicion of a possible collagen vascular disease. Radiographs of the knees were performed and documented Kellgren-Lawrence grade III medial compartmental osteoarthritic changes in both knees. There was no erosive lesion specific for inflammatory joint disease. In spite of 6 months of physical therapy and treatment with oral non-steroidal anti-inflammatory drugs, the pain continued and the patient elected to undergo left total knee arthroplasty (TKA) in April 2009, followed by right TKA in August 2010. The

patient experienced an uneventful recovery from both surgeries until 4 weeks after the left TKR when she presented to our clinic with a sudden onset of a high-grade fever (38.5°C), mild chest and abdominal pain with mild discomfort in her right knee. Blood testing was performed, the CRP was 25 mg/dL, and rheumatoid factor and anti-CCP (cyclic citrullinated peptide) were negative. A right-knee arthrocentesis was performed yielding 25 mL of slightly bloody fluid with a white blood cell count of 4500/μL and negative bacterial culture. Chest X-ray, chest CT, abdominal US, and electrocardiography revealed no abnormalities. The fever and chest pain continued for about 3 days after onset and then disappeared spontaneously. Three days after the onset of fever, the CRP fell to 1.0 mg/dL. Because she met the criteria for FMF based upon the Tel-Hashomer criteria [5], after informed consent was obtained, the DNA of the patient was extracted from her peripheral blood mononuclear cells. The coding exons and flanking intronic sequences of the *MEFV* gene were amplified by polymerase chain reaction (PCR). The sequences of the PCR primers are available on request. The PCR products were treated using an ExoSAP-IT kit (GE Healthcare, Amersham, UK) and then analyzed by direct sequencing with an ABI 3130 DNA sequencer (PerkinElmer, Foster City, CA). The L110P, E148Q, and M694I mutations were found in the patient. FMF was confirmed by the mutation in the hot spot of *MEFV*. Her younger brother was also diagnosed with FMF after the same gene mutations. Following FMF diagnosis, treatment with 1.0 mg/day colchicine was initiated and the episodes were successfully prevented.

Discussion

FMF is an autosomal recessive disease characterized by attacks of relapsing and self-limiting fever, peritonitis, pleuritis, and arthritis. FMF is seen more frequently among Turkish, Armenian, Jewish, and Arabic populations [11]. It is already known that mutation of the *MEFV* gene, which codes the protein called pyrin, causes FMF. The M694V, M694I, M680I, V726A, and E148Q mutations in *MEFV*, the gene responsible for FMF, account for most FMF cases in Mediterranean populations [13]. In Japan, M694I and E148Q are most frequently detected and recently, M680I have been identified [7]. Arthritis attacks are present in 50 to 70% of FMF cases, and they occur commonly as non-deforming acute monoarthritis affecting large joints of lower extremities such as the hip and knee. Arthritis generally lasts for 1 month [10, 12]. But in 5% of the cases, prolonged attacks of arthritis involving particularly the hip and knee can occur and cause permanent joint injury and deformities [6]. In some cases with the inflammatory joint disease like ankylosing spondylitis, those involved joints were severely destructed [3, 4, 9, 14]. To date, there have been no case reports of TKA in patients with FMF in Japan. From the specimen of synovium obtained during the TKA surgery, histological analysis based on H&E staining suggested only non-specific inflammation reaction (Fig. 1) without

Fig. 1. This specimen of synovium obtained during the TKR based stained with H&E demonstrates (arrow) a non-specific inflammation reaction. There is no evidence of lymphoid follicles or plasma cells suggestive of rheumatoid arthritis (bar = 100 μm).

evidence of lymphoid follicles or plasma cells which are rather specific to rheumatoid arthritis.

Because of rare occurrence, FMF might go unrecognized in a post-op fever workup. There are no specific laboratory tests to diagnose FMF. During the attacks, serum CRP, fibrinogen, amyloid A, ESR, and leukocyte count increase [1]. After the diagnosis of FMF was established in this patient, prednisolone was discontinued and colchicine was started with no recurrence of symptoms for 3 years. We believe this is the first report of FMF diagnosed using DNA analysis in a patient with the fever of unknown origin following the TKA.

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Disclosures

Conflict of Interest: Sumito Kawamura, MD, PhD, Kazunaga Agematsu, MD, Daisuke Kawamura, MD, Goroh Kawamura, MD, Koji Suzuki, MD, and Michio Minami, MD have declared that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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