Familial Mediterranean Fever developing in a Japanese kidney transplant recipient

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Abstract Familial Mediterranean Fever (FMF) is an auto-inflammatory disease characterized by periodic febrile episodes and sterile polyserositis and is extremely rare in Asian populations. Here, we report a case of FMF in a 61-year-old Japanese man who received a kidney transplant 31 years ago but had to re-start hemodialysis. Although kidney function had been stable since his initial transplant, serum creatinine levels had been increasing over the 2 years prior to his presentation at our hospital, and a periodic fever developed at the same time. Uremic symptoms were observed, and hemodialysis was re-started, prompting the patient to choose to undergo a second kidney transplantation. We re-checked his medical history and conducted further physical examinations. Given that the patient had previously undergone an operation for olecranon bursitis in which pericardial effusion had been identified, we considered the possibility of FMF and conducted a genetic test, which identified the E202Q heterozygous mutation in the MEFV gene. The patient was therefore diagnosed with variant FMF. To our knowledge, this is the first report of a Japanese kidney transplant recipient being diagnosed as an FMF variant. We describe the relationship

of FMF and kidney transplantation in terms of prognosis and important points to note for treatment.

Keywords Kidney transplantation · Recipient · Familial Mediterranean Fever

Introduction

Familial Mediterranean Fever (FMF) is an auto-inflammatory disease characterized by periodic febrile episodes and sterile polyserositis. The cause of FMF is a mutation in the Mediterranean fever (MEFV) gene, which is located on the short arm of chromosome 16 and consists of 10 exons [1]. The MEFV gene transcribes pyrin, which causes an inflammatory response to protect against infection [2]. FMF is mainly observed in Mediterranean populations, such as Armenian, Arab, non-Ashkenazi Jewish, and Turkish populations [1], and is extremely rare in Japan, with a recent national survey estimating only 300 FMF patients in the country [2].

Colchicine is the first-choice treatment for FMF and is effective in 90 % of Japanese FMF patients [2]. Other treatments for FMF include TNF- α inhibitors [3, 4], IL-1 receptor blockers [5], and thalidomide [4]. In contrast, steroid and calcineurin inhibitors (CNIs), which are commonly used in transplantation, are not effective for FMF. The prognostic factor of FMF is the development of amyloid A (AA) amyloidosis, which usually involves the kidneys and eventually results in kidney failure. The risk factors for the development of AA amyloidosis include MEFV mutations (particularly the M694V mutation in exon 10), ethnicity, presence of family history, male gender, and low response to colchicine therapy [6]. Kidney transplantation for FMF-induced AA amyloidosis is not a

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contraindication, and prognosis of kidney transplantation in FMF patients is the same as in non-FMF patients [7].

To our knowledge, this is the first report of FMF developing in a Japanese kidney transplant recipient.

Case

A 61-year-old man had received a living kidney transplant from his mother in 1982 at age 30 in Nagoya Daini Red Cross Hospital and has received long-term care even now at the same hospital. Primary cause of End-stage kidney disease (ESKD) was not detected. Graft function was stable [serum creatinine (s-Cr) 1.0–1.7 mg/dl] following transplantation but gradually became impaired from 2011, and a graft biopsy was taken when s-Cr reached 2.5 mg/dl. No rejection, CNI toxicity, or viral infection was detected by light microscopy. As the glomerulus was not included in immunofluorescence specimens, we could not completely exclude recurrence or de novo glomerular nephritis. In 2011, the patient began to experience periodic fever (38–39 °C, duration of 1–5 days, cycle of 1–3 months) accompanied by elevated levels of inflammatory markers. Several potential causes of fever, such as infection, malignancy, and collagen disease, were ruled out. In February 2013, he reached an s-Cr level of 6 mg/dl and developed leg edema, pleural effusion, and uremic symptoms. Hemodialysis was re-started accordingly. As a second kidney transplantation from his wife was being considered, the reoccurrence of fever of unknown origin (FUO) was examined.

The patient had no family history of any kidney disease or FUO, and his personal history of illness included living kidney transplantation at age 30, pneumonia and operation of lumbar spinal canal stenosis at age 58, and operation of left olecranon bursitis at age 60. He was taking an oral administration of methylprednisolone (6 mg) and cyclosporine (CyA) (100 mg) for maintenance of immunosuppression, and valsartan (80 mg), fluvastatin (60 mg), amlodipine (7.5 mg), carvedilol (20 mg), lansoprazole

(15 mg), and furosemide (20 mg). He had never lived in or visited any infectious pandemic areas or the Mediterranean.

The findings for vital signs at admission for re-initiation of hemodialysis were as follows: blood pressure (156/79 mmHg), heart rate (86 bpm), body temperature (37.5 °C; but sharply increased to 38.6 °C at Day 4 of hospitalization). Significant findings on physical examination included bilateral edema and erythema in left lower extremity during fever. Imaging studies revealed pericardial and pleural effusion and left olecranon bursitis (Fig. 1). Laboratory tests showed elevations in the following inflammatory markers: white blood count (13,600/ μ l), ESR (83 mm/h), C-reactive protein (CRP) (5.05 mg/dl) and serum amyloid A (SAA) (576 μ g/ml). Liver enzymes, tumor-associated markers, IL-2 receptor antibody, rheumatoid factor and anti-neutrophil cytoplasmic autoantibody (ANCA) titers were normal. Urinalysis showed no microscopic hematuria or leukocyturia in urinary sediment, and 3.4 g/g Cre of albuminuria which was constituted the vast majority of proteinuria. The findings from additional examinations to determine the cause of FUO were as follows: electrocardiogram was normal, echocardiography revealed pericardial effusion, Congo red staining of abdominal fat pad biopsy was negative, upper and lower endoscopy showed no specific changes (no malignancy), no inflammation was noted on PET-CT and gallium-scintigraphy, and blood and urine cultures were negative. The details of clinical course of periodic fever after onset are shown in Table 1.

Several potential causes of FUO—such as malignancy, collagen disease, and infection—were excluded. FMF was suspected due to periodic fever lasting 1–5 days every 1–3 months with maximum temperature of 39 °C, elevated inflammatory markers during the febrile period but not the afebrile period, erythema in the left lower extremity during the febrile period pericardial effusion, and left olecranon bursitis. However, as typical symptoms such as peritonitis and mono-arthritis were not observed, we tried to diagnose FMF by performing genetic testing. The patient fulfilled the diagnostic criteria of FMF (Fig. 2), and a mutation was

Fig. 1 Pericardial and pleural effusion on chest CT (*above*) and left olecranon bursitis on MRI (*below*)

Table 1 Clinical course of fever, inflammation markers, and symptoms

Date	11/07/25	11/08/03	11/08/19	11/09/30	11/10/06	11/11/20	12/05/22	12/12/23	13/02/16
Max. BT (°C)	38.2	38.9	39.4	38.0	38.0	38.0	39.0	39.0	38.6
Febrile duration (days)	N/A	3	5	N/A	1	4	N/A	3	5
WBC (count/ μ l)	24,300	25,300	14,100	19,000	22,900	13,000	24,500	29,300	13,600
CRP (mg/dl)	13.9	9.44	1.56	0.89	10.9	2.43	2.04	6.95	5.05
S-Cr (mg/dl)	2.6	2.7	2.0	2.2	2.2	2.1	3.7	5.2	4.5

Max. BT maximum body temperature during one febrile session, WBC white blood count, CRP C-reactive protein, S-Cr serum creatinine, N/A not available

Fig. 2 Diagnostic criteria for FMF. Tel-Hashomer criteria (left) [12]. Clinical Guidelines for FMF (right), referenced from the Study Group of Familial Mediterranean Fever for Research on Intractable Diseases, Health and Labour Science Research Grants, Ministry of Health, Labour and Welfare of Japan

【Tel-Hashomer criteria】	【Clinical Guideline for FMF, 2011 in Japan.】
Major Criteria typical attack 1. peritonitis (non-localized) 2. pleuritis (unilateral) or pericarditis 3. mono-arthritis (hip, knee, ankle) 4. fever (more than 38°C) Minor Criteria atypical attack is including one or more symptoms(below) 1. pleuritis or pericarditis 2. mono-arthritis (hip, knee, ankle) 3. lower extremities pain after exercise 4. good response to colchicine therapy A diagnosis of FMF was determined if the patients exhibited 1 or more major criteria or, 2 or more minor criteria.	Major Criteria A fever of 38 degrees or above lasting for between 12 hours and three days, more than three times Minor Criteria 1. Concomitant symptoms with the fever a. abdominal pain due to non-localized peritonitis b. chest and back pain due to pleuritis c. arthritis (hip, knee, ankle) d. pericarditis e. testicular vaginalitis f. head ache due to meningitis 2. During the febrile periods, the inflammatory response such as CRP and SAA are increased, but during afebrile period, there are disappeared. 3. Preventative administration of colchicine either eliminated or reduced the attacks. A diagnosis of FMF was determined if the patients exhibited the major criterion and 1 or more minor criteria.

detected in the MEFV gene (in exon 2, E202Q/normal: heterozygous). However, FMF was unlikely due to the late age of onset, lack of family history and peritonitis, long febrile duration (5 days), and atypical arthritis (serositis). We therefore diagnosed the patient with an FMF variant (Fig. 3).

Subsequent to a second kidney transplantation at age 61, the patient was administered colchicine therapy to relieve the symptoms of FMF and prevent secondary amyloidosis. Colchicine administration was continued after the second kidney transplantation. Dosage was reduced to 0.5 mg once daily due to administration of CyA as an immunosuppressant. Six months after the second transplantation, the patient had good renal function and no proteinuria, with only one episode of fever, which resulted in an increase in colchicine dosage. He subsequently suffered severe

diarrhea and bone marrow suppression. Colchicine was terminated and will be resumed when these symptoms improve.

Discussion

To our knowledge, this is the first report of FMF in a Japanese kidney transplant recipient. As FMF is extremely rare in Japan there are several noteworthy points in this case. The first point concerns the determination of the primary cause of ESKD and whether it was AA amyloidosis. The patient experienced no episodes of fever or typical symptoms of FMF before first transplantation. FMF-induced AA amyloidosis was therefore considered unlikely. Unfortunately, information regarding the primary

Fig. 3 Algorithm for atypical FMF (FMF variant). *MEFV* Mediterranean fever. This algorithm was developed by the Study Group of Familial Mediterranean Fever for Research on Intractable Diseases, Health and Labour Science Research Grants, Ministry of Health, Labour and Welfare of Japan

cause of ESKD was insufficient because the medical record was destroyed.

The second point regards AA amyloidosis potentially causing graft loss. To clarify this point, Congo red staining was conducted on a biopsy specimen of the transplanted graft taken in 2011, and no positive staining was observed. We therefore did not consider AA amyloidosis to be the cause of graft loss. Instead, we considered graft loss to be due to severe chronic tubulointerstitial damage from arteriosclerosis and shattered grafts, as determined by biopsies. Amyloidosis generally develops in approximately 50–60 % of untreated FMF cases. Further, AA amyloidosis is the leading cause of FMF-induced kidney disease, but polyarteritis nodosa and purpura nephritis have also been reported [8]. In Turkey, approximately 3 % of ESKD cases are caused by amyloidosis, the majority of which are induced by FMF [9]. In Japan, however, only 0.3 % of ESKD cases are caused by amyloidosis [10]. The majority of amyloidosis cases in Japan are considered to be amyloid light-chain (AL) amyloidosis. As such, very few patients present with FMF in Japan, and according to the Japanese FMF surveillance, only one case of FMF-induced (AA amyloidosis) ESKD has been reported [2].

The third point concerns the prognosis of kidney transplantation in FMF patients, since the present case received a second kidney transplant from his wife. The clinical outcome of kidney transplantation caused by AA amyloidosis (FMF) is similar to that of other causes of ESKD [7]. Indications for kidney transplant should be determined based on organ involvement (particularly the heart and gastrointestinal tract), which affects the patient's

prognosis. Continued colchicine therapy subsequent to transplantation can prevent symptoms such as fever and the onset of AA amyloidosis [7]. Consequently, colchicine administration to kidney transplant recipients with FMF might be the optimal treatment [7].

Finally, the following should be considered with regard to kidney transplantation for FMF/amyloidosis. First, drug interactions between CyA and colchicine, inhibition of CYP3A4 metabolism, and inhibition of P glycoprotein, exacerbate colchicine toxicity. Colchicine toxicity includes diarrhea, nausea, abdominal pain, rhabdomyolysis, bone marrow suppression, depilation, and azoospermia. Second, a reduced dose of colchicine is required in cases of liver or kidney dysfunction, as these conditions also exacerbate colchicine toxicity. Third, stomach excretion is delayed in cases of gastrointestinal amyloidosis, leading to unstable concentrations of immunosuppressants [11].

Conclusion

To our knowledge, this is the first case of FMF variant in Japan, which developed in a Japanese kidney transplant recipient. Neither the primary cause of ESKD nor graft loss was due to FMF-induced AA amyloidosis. However, colchicine treatment continued following transplantation to alleviate symptoms and prevent kidney involvement resulting from AA amyloidosis. Colchicine should be administered to kidney transplant recipients with care due to potential drug interactions with CyA, and the required dose should be adjusted in patients with liver and kidney impairment.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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