

Overlap Syndrome between Familial Mediterranean Fever and Tumor Necrosis Factor Receptor-Associated Periodic Syndrome in a Lupus Patient

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Autoinflammatory diseases represent an expanding spectrum of genetic and non-genetic inflammatory diseases characterized by recurrent episodes of fever and systemic inflammation, affecting joints, skin and serosal surfaces. Familial Mediterranean fever (FMF) is the most common autosomal recessive hereditary autoinflammatory disease. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant hereditary autoinflammatory disease. They share some clinical manifestations such as a periodic fever and skin rash. We present here the association of FMF with TRAPS in a systemic lupus erythematosus (SLE) patient. A 54-year-old SLE patient with recurrent attacks of fever, arthritis, and skin rashes was referred to our hospital. She had been diagnosed with lupus nephritis at 19 years old. Her lupus nephritis was controlled by steroid treatments; however, since childhood she has suffered from recurrent episodes of periodic fever, abdominal pain, arthritis, and erythematous skin rashes. An initial diagnosis of FMF was suspected based on the genetic analysis, showing the compound heterozygous L110P/E148Q mutations in the *MEFV* gene that is responsible for FMF. Her symptoms responded to colchicine, but the febrile attacks were not completely resolved. Therefore, genetic testing for TRAPS was performed. The results revealed a heterozygous T61I mutation in the *TNFRSF1A* gene that encodes tumor necrosis factor- α receptor and is responsible for TRAPS. The patient was diagnosed with overlapping FMF and TRAPS, in addition to SLE. This is the first report of SLE associated with both FMF and TRAPS.

Keywords: autoinflammatory disease; familial Mediterranean fever; *MEFV* gene; systemic lupus erythematosus; tumor necrosis factor receptor-associated periodic syndrome

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Introduction

Autoinflammatory diseases represent an expanding spectrum of genetic and non-genetic inflammatory diseases characterized by recurrent episodes of fever and systemic inflammation, affecting joints, skin and serosal surfaces (Henderson and Goldbach-Mansky 2010). The first condition recognized as autoinflammatory was the hereditary periodic fever syndrome. Familial Mediterranean fever (FMF) is the most common autosomal recessive, hereditary, autoinflammatory disease caused by *MEFV* gene mutations (Ben-Chetrit and Levy 1998). FMF attacks last 1-3 days and are characterized by polyserositis and colchicine responsiveness (Savic et al. 2012). Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an auto-

somal dominant autoinflammatory disease, caused by mutations in the *TNFRSF1A* gene encoding the 55-kDa tumor necrosis factor- α (TNF- α) receptor, and characterized by febrile episodes involving abdominal pain, pleurisy, myalgia, skin rashes and arthritis (McDermott et al. 1999). TRAPS attacks usually last more than 7 days and fail to respond to colchicine, but are responsive to steroids (Hull et al. 2002). Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease characterized by multisystem involvement and production of numerous autoantibodies (Ruiz-Irastorza et al. 2001). Autoinflammatory diseases and autoimmune diseases had been considered as distinct disease entities, but their similarities suggest that they might be considered as parts of a single spectrum of disease with an immune etiology, caused by changes in

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innate, or innate and adaptive, immune system homeostasis, respectively (Doria et al. 2012). In this case report, we describe a 54-year-old Japanese woman with lupus who presented with recurrent inflammatory attacks and an atypical clinical presentation, with mutations in the *MEFV* and *TNFRSF1A* genes.

Case Report

A 54-year-old woman who suffered from long-standing periodic fever was referred to our clinic for consultation in July 2012. She had suffered since the age of 13 from various inflammatory episodes including periodic fever lasting 5–7 days, arthralgia/arthritis, myalgia, erythematous rash, gastrointestinal symptoms, pharyngitis and tonsillitis. She underwent tonsillectomy at 11 years old and appendectomy because of acute abdomen at 17 years old.

At age 19 years, she was diagnosed with SLE and secondary Sjögren's syndrome in our hospital, based on a skin rash on the face, photosensitivity, non-erosive polyarthritis, proteinuria, bicytopenia (white blood cells $2,500/\mu\text{L}$, platelets $11.6 \times 10^4/\mu\text{L}$) with lymphopenia ($440/\mu\text{L}$) and elevated serum levels of anti-double-stranded-DNA antibodies and anti-nuclear antibodies ($\times 640$, normal $< \times 40$). Anti-Sjögren's syndrome A (anti-SSA) and anti-Sjögren's syndrome B (anti-SSB) antibodies were both positive with high titers. Renal biopsy specimens showed type V lupus nephritis (Fig. 1). Her clinical symptoms regressed after initiation of oral prednisolone 60 mg/day, with improvements in laboratory data; however, febrile attacks with polyarthritis and skin rash still occurred under maintenance steroid therapy.

When she visited our clinic, her symptoms were recurrent fever (up to 38°C) lasting 4–5 days, lymphadenopathy, splenomegaly, myalgia and swollen bilateral wrist joints.

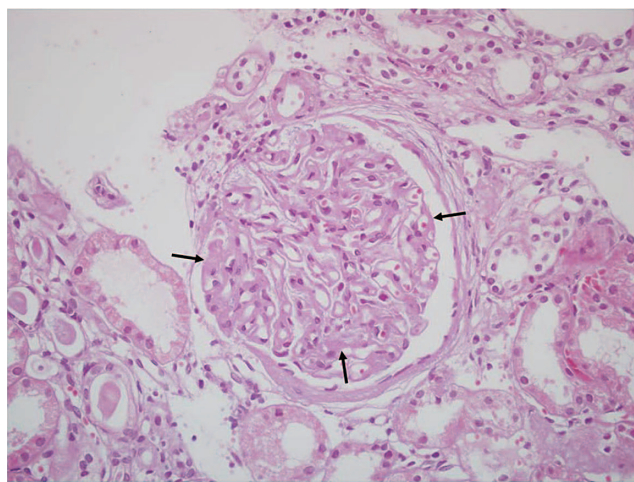


Fig. 1. Light microscopic findings of a renal biopsy specimen showing lupus glomerulonephritis.

A glomerulus shows a marked thickened capillary wall (diffuse membranous lesion; arrow) demonstrating lupus membranous glomerulonephritis (WHO class V). (Hematoxylin and eosin, $\times 250$).

Laboratory data did not indicate lupus disease activity (Table 1). The patient fulfilled Tel-Hashomer's diagnostic criteria for incomplete-type FMF (Livneh et al. 1997). DNA sequencing of the *MEFV* gene (exon 1–exon 10) was performed after obtaining informed consent, and compound heterozygous mutations (L110P/E148Q) were detected in exon 2 of the *MEFV* gene (Fig. 2), suggesting a diagnosis of FMF (Stojanov et al. 2004; Migita et al. 2012). Regular colchicine treatment was started, resulting in modest decreases in the intensity and frequency of febrile attacks. However, the attacks were not completely eradicated. *TNFRSF1A* gene (exon 1–exon 10) analysis was therefore also performed, and revealed that the patient was a heterozygous carrier of a T61I mutation in exon 3 of the *TNFRSF1A* gene (Fig. 2). The T61I mutation was reported in a Japanese patient with SLE (Ida et al. 2004). The *MEFV* and *TNFRSF1A* genes analysis was approved by the Ethics Committee of Nagasaki Medical Center. A diagnosis of an overlapping syndrome between FMF and TRAPS was considered. Her severe attacks were controlled with colchicine. However, a TNF blocker, etanercept, represents an exciting advancement in TRAPS treatment (Cantarini et al. 2012), with the ability to affect SLE activity (Costa et al. 2008), and may be recommended if and when necessary.

Discussion

Hereditary autoinflammatory diseases are characterized by spontaneous attacks of inflammation (Henderson and Goldbach-Mansky 2010). They include FMF and TRAPS. FMF is caused by mutations in *MEFV* gene (Savic et al. 2012) and TRAPS is caused by mutations in *TNFRSF1A* gene (Cantarini et al. 2012). We describe a Japanese patient with SLE who had FMF-like febrile episodes with abdominal pain, skin rash and arthralgia, and the patient was found to have co-existing *MEFV* and *TNFRSF1A* gene mutations. Some of the patient's clinical features differed from FMF, including prolonged febrile duration and partial colchicine responsiveness. Patients with overlap syndrome between FMF and TRAPS carrying mutations in both the *MEFV* and *TNFRSF1A* genes have recently been shown to have overlapping symptoms and to not respond well to standard therapy (Stojanov et al. 2004; Granel et al. 2007; Cantarini et al. 2008). Additionally, a rare occurrence of hyper-immunoglobulinemia D syndrome (HIDA) and TRAPS with defective *TNFRSF1A* shedding and partial response to standard therapy had been described (Arkwright et al. 2002). Interactions between mutated autoinflammatory genes may thus have produced the overlapping 'FMF-like' and 'TRAPS-like' symptoms seen in the present patient. This case report shows that mutations in the *MEFV* and *TNFRSF1A* genes can occur together in a single patient, resulting in a complex clinical condition, and affecting the patient's response to treatment.

FMF is an autosomal recessive disorder. However, up to 80% of Japanese FMF patients have been shown to have heterozygous or compound heterozygous *MEFV* mutations

Table 1. Laboratory Findings.

Peripheral blood		Serological tests	
Red blood cells	441 × 10 ⁴ /μl	C-reactive protein	< 0.30 mg/ml (< 0.30)
Hemoglobin	12.2 g/dl	Erythrocyte sedimentation rate	42 mm/hr
White blood cells	3,400/μl	IgG	1,680 mg/dl (900-2,000)
Neutrophil	62.6%	C3	74 mg/dl (86-160)
Monocyte	4.7%	CH50	53 U/ml (30-50)
Lymphocyte	31.8%	Anti-nuclear Ab	× 640 (Sp)
Eosinophil	0.6%	Anti-ds DNA Ab	9.3 U/ml (< 10)
Basophil	0.3%	Anti-ssDNA	481.5 U/ml (< 10)
Platelet	17.8 × 10 ⁴ /μl	Anti-RNP Ab	(-)
Blood chemistry		Anti-Sm Ab	(-)
Total protein	7.1 g/dl	Anti-SSA Ab	134.3 IU/ml (< 10)
Total bilirubin	0.6 mg/dl	Anti-SSB Ab	191.8 IU/ml (< 10)
Glutamic-oxaloacetic transaminase	31 IU/l (7-33)	Virological test	
Glutamic-pyruvic transaminase	24 IU/l (5-30)	HCV-Ab	(-)
Lactate dehydrogenase	207 IU/l (260-480)	HBsAg	(-)
Alkaline phosphatase	220 IU/l (80-250)	Urinalysis	
Creatinine kinase	126 IU/l (60-160)	Protein	(-)
Total cholesterol	217 mg/dl	Sugar	(-)
Blood urea nitrogen	12.3 mg/dl	Occult blood	(-)
Creatinine	0.9 mg/dl	Sediment	(-)
Alb	3.6 g/dl		
Na	142 mEq/l		
K	3.9 mEq/l		
Cl	103 mEq/l		

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

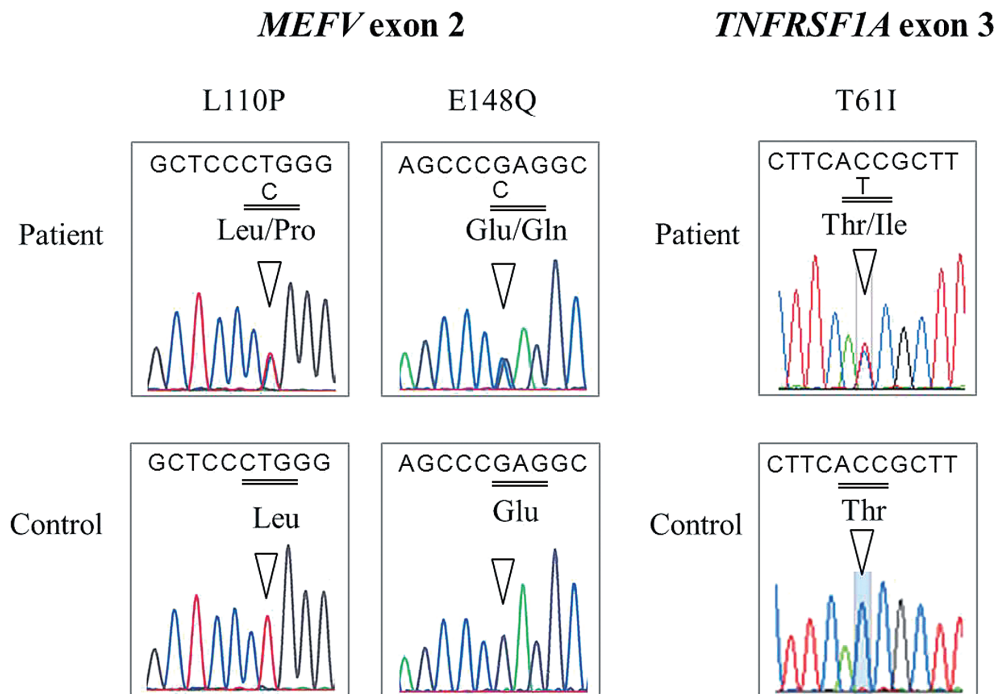


Fig. 2. Sequence analysis of the *MEFV* and *TNFRSF1A* genes in the present case.

DNA sequencing demonstrates the T-to-C transition in codon 110 of *MEFV* gene (exon 2), converting Leu to Pro, and the G-to-C transition in codon 148, converting Glu to Gln (left panels). Right panels show the C-to-T transition in codon 61 of *TNFRSF1A* gene (exon 3), converting Thr to Ile.

(Migita et al. 2012), sufficient to cause disease manifestations. Many studies have shown that heterozygous carriers of *MEFV* mutations can be symptomatic and suffer from febrile attacks, rashes and synovitis (Booty et al. 2009). Additionally, heterozygous mutations in exon 2 of the *MEFV* gene act as disease-severity modifiers in inflammatory diseases such as arthritis (Lachmann et al. 2006). Autoinflammatory gene mutations have also been described in patients affected with vasculitis; autoinflammatory gene mutations in these patients are known to modify disease severity, response to agents, and/or clinical manifestations (Atagunduz et al. 2003; Girisgen et al. 2012).

SLE is caused by multiple genetic and environmental factors. Polymorphisms in the *TNF- α* and *TNF-RII* genes increase susceptibility to SLE (Tsao 2000), while another TNF receptor molecule *TNFRSF1A* may also play a role in SLE susceptibility. The T61I mutation is considered to be a low-penetrance *TNFRSF1A* gene variant; however, the T61I variant has been reported in association with SLE in a Japanese TRAPS patient (Horiuchi et al. 2004; Ida et al. 2004). This suggests that pathophysiologic interactions between SLE and TRAPS cannot be excluded, and that T61I might be a contributing factor for SLE. The combination of *MEFV* mutations and T61I could theoretically lead to an increased inflammatory state that manifests as periodic inflammation within the spectrum of TRAPS and FMF. It appears difficult to categorize SLE as an autoinflammatory disorder. However, there is evidence that innate immunity or the autoinflammatory pathway plays a role in the initiation and perpetuation of autoimmunity including lupus (Aringer et al. 2013). It is possible that the abnormalities in the genes responsible for hereditary autoinflammatory diseases had contributed to the pathogenesis of SLE in this patient.

The long-term therapeutic strategy for lupus patients with TRAPS or FMF is currently unclear and needs to be evaluated carefully, given that anti-TNF- α therapy can exacerbate disease in SLE patients (Costa et al. 2008). Recent data showed that interleukin-1 inhibitors, such as anakinra and canakinumab, offer the most appropriate TRAPS treatment, given that etanercept has failed to induce complete disease remission and/or the normalization of acute phase reactants (Gattorno et al. 2008; Brizi et al. 2012).

In conclusion, we present a patient with SLE who also exhibited an overlap syndrome between FMF and TRAPS, with mutations in both the *MEFV* and *TNFRSF1A* genes. This case shows that mutations in *MEFV* and *TNFRSF1A* can occur in a patient with autoimmune disease.

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Conflict of Interest

The authors declare no conflict of interest.

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