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【 CASE REPORT 】

# A Rare Case of Cryopyrin-associated Periodic Syndrome in an Elderly Woman with *NLRP3* and *MEFV* Mutations

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**Abstract:**
We herein report a case of a 75-year-old woman who presented with a low-grade fever, repeated cold-induced urticaria, and painful leg edemas with neutrocytosis. Because her mother also had cold-induced urticaria and her skin lesions histologically showed neutrophilic dermatitis, we suspected that she had familial cold autoinflammatory syndrome, a subtype of cryopyrin-associated periodic syndromes. Sequencing of the *NLRP3* and *MEFV* genes revealed that she carried both the p.A439V missense mutation and p.E148Q homozygous mutation, which is commonly detected in familial Mediterranean fever patients. The administration of colchicine reduced the frequency and severity of her skin rash and leg edema.

**Key words:** elderly, FCAS, CAPS, MEFV, A439V, E148Q

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## Introduction

Cryopyrin-associated periodic syndromes (CAPS) are a group of three hereditary febrile syndromes: familial cold autoinflammatory syndrome (FCAS); Muckle-Wells syndrome (MWS); and neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological, cutaneous, and articular syndrome (CINCA), which are caused by mutations in *NLRP3* (formerly known as *CIAS1*) (1). The altered gene product cryopyrin regulates the production of interleukin (IL)-1β through the formation of a macromolecular complex termed the inflammasome, which causes the inflammatory manifestations in CAPS (1, 2).

FCAS is typically genetically inherited as an autosomal dominant trait. It is the least severe phenotype of CAPS and is characterized by recurrent episodes of chills, a fever, headache, arthralgia, conjunctivitis, and urticaria-like rash in response to generalized cold exposure (3). MWS is characterized by progressive sensorineural deafness as well as recurrent episodes of urticaria-like rash, a fever, and arthralgia. NOMID/CINCA has the most severe phenotype with chronic aseptic meningitis, characteristic arthropathy, and rash. In Japan, the estimated number of patients with CAPS is approximately 100 (4).

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disease observed in Mediterranean populations and is characterized by recurrent febrile episodes and inflammation in the form of sterile polyserositis (5, 6). The *MEFV* gene is known to be responsible for FMF; most of the more severe disease-associated FMF mutations are located in exon 10 of the gene, and a smaller group of milder variants is found in exon 2, such as E148Q (7).

We herein report the first Japanese case of CAPS compli-

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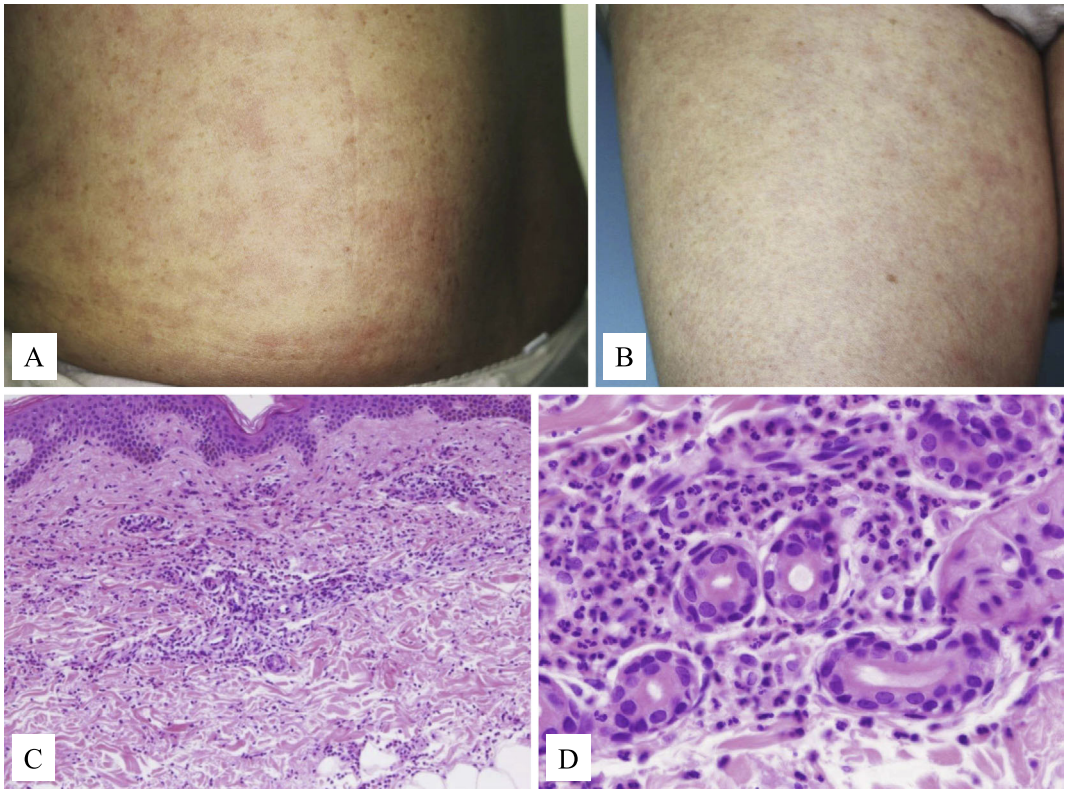


**Figure 1.** **A, B: Skin findings on admission. Many erythemas about 1 cm in size were scattered on the upper and lower extremities and trunk (A: abdomen, B: anterior surface of right thigh). C, D: Photomicrographs of the skin biopsy of the right femoral region (Hematoxylin and Eosin staining, C: ×100, D: ×400). A band of inflammatory cell infiltration consisting mainly of neutrophils was observed in all layers of the dermis, especially around adnexa, such as the small blood vessels and sweat glands.**

cated with *MEFV* genetic abnormalities that was relieved by colchicine treatment.

## Case Report

A 75-year-old-woman was referred by a general practitioner to our hospital for a low-grade fever and an elevated C-reactive protein (CRP) level. Previous examinations performed to determine the cause of inflammation had been inconclusive.

A physical examination revealed a good general condition, normal body temperature (36.7℃, which was higher than her usual body temperature of 35.5°C), and tenderness in the lower legs with slight skin edema. A neurological examination revealed no pathological findings. Because the skin lesions on the legs were suspected to be bacterial cellulitis, some antibiotics, including cefdinir, cefditoren pivoxil, levofloxacin, ceftriaxone, meropenem, and faropenem, were administered, but they were ineffective.

One day, she visited us with generalized pale erythematous macules without itching or pyogenic abscesses (Fig. 1). Based on her testimony and the diagnosis by her primary care physician, we recognized the skin lesions as "cold-induced urticaria," because they had generally appeared after exposure to cold since she was a teenager. She revealed that her mother also used to develop similar skin lesions after exposure to cold.

A peripheral blood examination at that time revealed an elevated white blood cell (WBC) count (37,200/μL), neutrophils (88%), and serum CRP level (8.01 mg/dL). Serum amyloid A protein was 149.2 μg/mL (reference range <8.0 μg/mL) (Table). Computed tomography of the neck, chest, abdomen, and pelvis revealed no obvious abnormalities. Blood cultures were negative.

A skin biopsy of the urticarial rash of the right thigh was immediately performed, and the pathological diagnosis was "neutrophilic dermatitis" because a band of inflammatory cell infiltration consisting mainly of neutrophils was observed in all layers of the dermis, especially around the adnexa, such as small blood vessels and sweat glands (Fig. 1). The urticarial rash spontaneously disappeared, and the WBC count decreased to 13,800/μL the following morning without any treatment.

A detailed enquiry revealed that she had also had episodes of repeated conjunctivitis without any particular triggers since an early age. Because of her clinical course and familial history of cold-induced urticarial skin rash, we suspected a diagnosis of FCAS. The results of the sequencing of exon 3 of the *NLRP3* gene were received six months later, showing that she carried the p.A439V missense muta-

**Table. Laboratory Findings on Admission.**

| Peripheral blood counts | | Serological examinations | |
|---|---|---|---|
| WBC | 37,200 /μL | CRP | 8.01 mg/dL |
| (Neu 88%, Lym 11%, Mon 1%) | | sIL-2R | 862 μg/dL |
| RBC | $353\times10^4$ /μL | Ferritin | 104 ng/mL |
| Hb | 11.2 g/dL | ANA | 160× (SP) |
| Hct | 33.6 % | Anti-Sm | 0.7 IU/mL |
| Platelets | $46.2\times10^4$ /μL | Anti-RNP | 8.9 index |
| ESR | 58 mm/h | Anti-SS-A | 1.2 index |
| Biochemistry | | Anti-SS-B | 1.1 index |
| Total protein | 7.9 g/dL | Anti-ds-DNA | 4.8 index |
| Albumin | 4.2 g/dL | Anti-Scl-70 | 2.1 index |
| AST | 31 IU/L | Anti-CCP | 0.2 U/mL |
| ALT | 19 IU/L | MPO-ANCA | <1.0 EU |
| LDH | 301 IU/L | PR3-ANCA | <1.9 EU |
| γ-GTP | 22 IU/L | Laboratory tests for infections | |
| BUN | 27 mg/dL | Blood cultures | (-) |
| Creatinine | 1.02 mg/dL | T-SPOT. TB assay | (-) |
| CK | 94 IU/L | Mycoplasma antibody | <40× |
| Urinalysis | | β-D- glucan | 7.1 pg/mL |
| gravity | 1.016 | Candida antigen | (-) |
| pH | 5 | Aspergillus antigen | 0.2 ng/mL |
| protein | (-) | Cryptococcus antigen | (-) |
| sugar | (-) | | |
| keton | (-) | | |
| Occult blood | (+) | | |
| RBC | 3-4/HPF | | |
| WBC | 3-4/HPF | | |

WBC: white blood cell count, Neu: neutrophil, Lym: lymphocyte, Mon: monocyte, RBC: red blood cell count, Hb: hemoglobin, Ht: hematocrit, ESR: erythrocyte sedimentation rate, AST: asparate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ-GTP: gamma-glutamyl transpeptidase, BUN: blood urea nitrogen, CK: creatine kinase, HPF: high-power field, CRP: C-reactive Protein, sIL-2R: soluble interleukin-2 receptor, ANA: anti-nuclear antibody, SP: speckled pattern, Anti-Sm: Anti-Smith antibody, Anti-RNP: Anti-U1 ribonucleoprotein antibody, Anti-SS-A: Anti-Sjögren's syndrome A antibody, Anti-SS-B: Anti-Sjögren's syndrome B antibody, Anti-ds-DNA: Anti-double stranded DNA antibody, Anti-Scl-70: Anti- Scl-70 antibody, Anti-CCP Ab: Anti-cyclic citrullinated peptide antibody, MPO-ANCA: Myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: Proteinase3-anti-neutrophil cytoplasmic antibody, SAA: Serum amyloid A protein

tion, which is known to be associated with FCAS (Fig. 2); therefore, she was diagnosed with FCAS.

Until the diagnosis of FCAS was confirmed, we observed her symptoms without treatment for the first four months. She developed no severe symptoms; however, the low-grade inflammation and tenderness in the lower legs with slight skin edema still persisted. Although she did not meet the Tel Hashomer criteria (8), we also suspected a diagnosis of the "atypical" or "incomplete" form of FMF. We sequenced exon 10 of the *MEFV* gene, which revealed that she also carried the p.E148Q homozygous mutation associated with FMF mutations (Fig. 2). Colchicine administration was started, which ameliorated her low-grade fever and tenderness in the lower legs with slight skin edema.

We suggested that she possibly had FCAS as well as the "atypical" or "incomplete" form of FMF. Treatment with canakinumab, a neutralizing antibody to IL-1β that has been shown to be effective in treating FCAS, was not administered because of its high cost and possible side effects, given her symptoms were mild.

She has since been taking oral colchicine (0.5-1.0 mg, daily), and she developed only a mild skin rash after exposure to the cold, with a mild elevation in CRP levels (Fig. 3).

## Discussion

We encountered a case of urticaria-like rash induced by cold exposure and unexplained inflammation with mutations in genes associated with both CAPS and FMF, which is very rare and has probably not been reported in Japan.

CAPS are extremely rare and are estimated to occur at a rate of 1:1,000,000; around 50 people have been diagnosed with CAPS in Japan. FCAS is the mildest subtype of CAPS

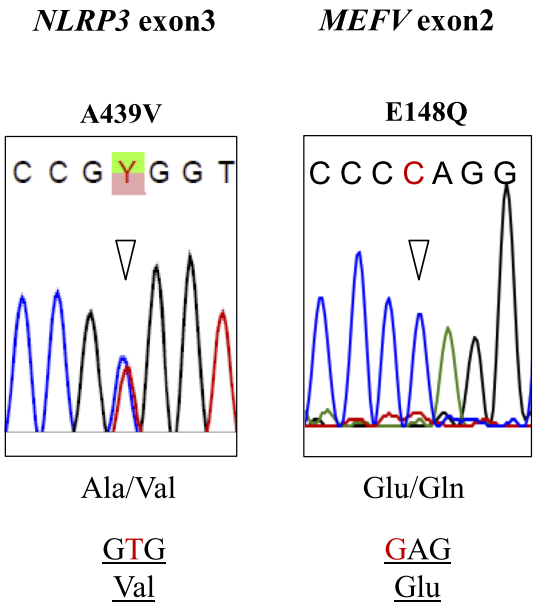


**Figure 2.** **A: The *NLRP3* gene analysis in the present case; the A439V heterozygous mutation, the C to T transition in codon 439 converted from alanine (A) to valine (V). Y means a mixed base of C and T. B: The *MEFV* gene analysis in the present case; the E148Q homozygous mutation, in which the G to C transition in codon 148 converted from glutamic acid (E) to glutamine (Q).**

and is the most strongly associated with cold stimuli (1, 3). Most cases of CAPS are considered to occur in early childhood, and this is the first case of late-onset CAPS, being diagnosed at 75 years of age based on recurrent episodes of urticaria-like rash induced by cold exposure and conjunctivitis, a family history of cold-induced urticaria, a histological diagnosis of neutrophilic dermatitis from biopsies of the urticarial sites, and the results of genetic testing.

Neutrophilic urticarial dermatosis (NUD) is thought to be a cutaneous marker of autoinflammation, and NUD with perieccrine involvement strongly indicates the presence of CAPS (9). Given the importance of neutrophil-mediated processes in autoinflammatory conditions, autoinflammation might play an important role in neutrophil-predominant skin diseases (10).

In the present case, the diagnosis of FCAS was delayed because of the rarity of the disease and the minor clinical manifestation at presentation. Many patients with mild symptoms might remain undiagnosed; therefore, FCAS needs to be considered in the differential diagnosis of adults.

CAPS are caused by mutations concentrated in exons 3, 4, and 6 of *NLRP3*. In this case, the heterozygous A439V mutation, which is regarded as the genetic aberration of FCAS and detected in about 10% of all patients with CAPS, was recognized. This mutation has been reported to be frequently associated with a non-neurological phenotype (11) and a heterogeneous clinical spectrum of FCAS/MWS-

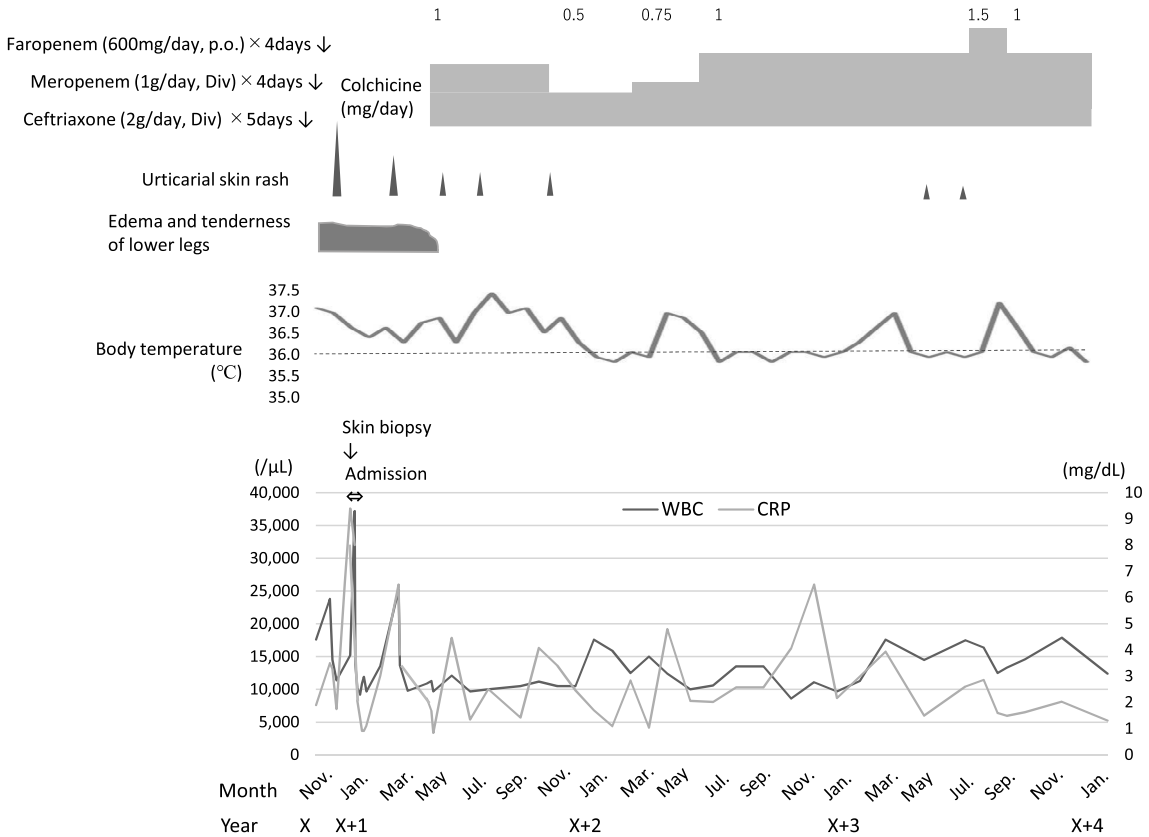


**Figure 3.** **The clinical course. Div: drip infusion in vein, p.o.: per os**

overlap syndrome and to be positively correlated with skin rash and eye diseases (12). As such, further attention needs to be paid to such patients to check for the exacerbation of the condition and ocular symptoms in the future.

In contrast, FMF is the most common form of hereditary periodic fever syndrome, with more than 10,000 patients worldwide and an estimated total of approximately 300 in Japan (13). FMF is an autoinflammatory disease caused by a defect in pyrin that blocks the function of inflammasome. Paroxysmal fever and its associated symptoms are characterized by severe pain due to serositis. FMF is caused by an autosomal and often homozygous recessive mutation in *MEFV*, but the mechanism underlying its development is not yet known. Other factors are thought to be involved in the development of FMF because of the lack of high penetrance and, in some cases showing typical symptoms of FMF, the lack of disease-related mutations in *MEFV* (5, 7).

Although the Tel Hashomer criteria are useful for achieving a diagnosis, not all patients completely meet the criteria. The typical genetic mutations are noted in exon 10 (M6801, M694V and M6941, V726A), but the relationship between FMF and genetic polymorphisms in exons 2 and 3 of *MEFV*, such as the EI48Q, P369S, and R408Q mutations, is not yet clear (14). These gene polymorphisms are found in about 10% of healthy Japanese individuals (15-17). Furthermore, the disease is less severe and the ratio of patients responding completely to colchicine higher in FMF patients with E148Q/E148Q mutations than in those with other *MEFV* mutations (18). Thus, MEFV exon 10 mutations are associated with the more typical FMF phenotype than other mutations. In contrast, more than half of the Japanese FMF patients without MEFV exon 10 mutations were found to present with an atypical FMF phenotype, indicating that Japanese FMF patients tend to be divided into two phenotypes based on variation in MEFV mutations (13). As indicated in the Tel Hashomer criteria, a typical FMF attack is defined as an episode lasting 12 hours to 3 days with a fever accompanied by peritonitis, pleuritis, or monoarthritis of the hip, knee, or ankle. In contrast, an incomplete attack is characterized by the following features: temperature of less than 38℃; an attack duration longer or shorter than the specified periods (12 hours to 3 days) but not shorter than 6 hours or longer than a week; localized abdominal signs; or an atypical distribution of arthritis (13).

In our case, the homozygous E148Q mutation was present, but the patient did not meet the Tel Hashomer criteria. The symptoms of her tenderness in the lower legs with slight skin edema might have been caused by the atypical FMF, as colchicine was effective, when it is usually not effective for the treatment of CAPS. We therefore diagnosed her condition as the coexistence of atypical FMF and FCAS.

To our knowledge, this is the first Japanese case of coexistent *NLRP3* and *MEFV* mutations manifesting as both CAPS and FMF. Previously, only two cases have been reported worldwide (19, 20). However, some patients diagnosed with FMF have been reported to show symptoms similar to those of CAPS (a cold exposure-related fever and urticarial rash) with *MEFV* mutations detected but *NLRP3* mutations either absent or not tested (21, 22). Furthermore, in patients having neutrophilic skin lesions of Sweet's syndrome, the mutations in *MEFV* have been described as similar to those in patients with FMF (23, 24). In addition, *MEFV* mutations have been found in a wide variety of autoinflammatory diseases, such as inflammatory bowel disease and Behçet's disease (25, 26), suggesting that *MEFV* mutations might also affect the severity of these diseases. Taken together, these findings suggest that CAPS and FMF are based on some common mechanism, as it was unlikely that these two rare diseases coincidentally coexisted.

In conclusion, we herein report an elderly female patient with *NLRP3* and *MEFV* mutations. Her conditions suggested FCAS, but colchicine was effective in resolving her symptoms. The two gene mutations might have interacted with each other, leading to the manifestation of the disease.

**The authors state that they have no Conflict of Interest (COI).**

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