CASE REPORT

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

Seiko Nakamichi, Tomoki Origuchi, Shoichi Fukui, Aya Yoda, Hiroshi Matsubara, Yuki Nagaura, Ryuta Nishikomori, Kuniko Abe, Kiyoshi Migita, Noriho Sakamoto, Atsushi Kawakami, Yoshiyuki Ozono and Takahiro Maeda

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-
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°C, 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 adnexa, such as the small blood vessels and sweat glands.

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-
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 the p.E148Q homozygous mutation associated with 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

### Table. Laboratory Findings on Admission.

| Peripheral blood counts | Serological examinations |
|-------------------------|-------------------------|
| WBC                     | CRP                     |
| 37,200 /μL              | 8.01 mg/dL              |
| (Neu 88%, Lym 11%, Mon 1%) | sIL-2R                 |
| 353×10^6 /μL            | 862 μg/dL               |
| Hb                      | Ferritin                |
| 11.2 g/dL               | 104 ng/mL               |
| Hct                     | Anti-Sm                 |
| 33.6 %                  | 0.7 IU/mL               |
| Platelets               | Anti-RNP                |
| 46.2×10^4 /μL           | 8.9 index               |
| ESR                     | Anti-SS-A               |
| 58 mm/h                 | 1.2 index               |
| Biochemistry            | Anti-SS-B               |
| Total protein           | 1.1 index               |
| 7.9 g/dL                | Anti-ds-DNA             |
| Albumin                 | 4.8 index               |
| 4.2 g/dL                | Anti-Scl-70             |
| AST                     | 2.1 index               |
| 31 IU/L                 | Anti-CC                 |
| ALT                     | 0.2 U/mL                |
| 19 IU/L                 | MPO-ANCA                |
| LDH                     | <1.0 EU                 |
| 301 IU/L                | PR3-ANCA                |
| γ-GTP                   | <1.9 EU                 |
| 22 IU/L                 | Laboratory tests for infections |
| BUN                     | Blood cultures          |
| 27 mg/dL                | (-)                     |
| Creatinine              | T-SOT. TB assay         |
| 1.02 mg/dL              | (-)                     |
| CK                      | Mycoplasma antibody     |
| 94 IU/L                 | <40x                    |
| Urinalysis gravity      | β-D-glucan              |
| 1.016                   | 7.1 pg/mL               |
| pH                      | Candida antigen         |
| 5                       | (-)                     |
| protein sugar keton     | Aspergillus antigen     |
| (-)                     | 0.2 ng/mL               |
| Occult blood RBC        | Cryptococcus antigen    |
| 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: aspartate 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
Figure 2. A: The \textit{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 \textit{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).

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