SHORT COMMUNICATION

Cryopyrin-associated Periodic Syndrome in a Family with *NLRP3* A441V Mutation

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Cryopyrin-associated periodic syndrome (CAPS) is a rare autoinflammatory syndrome caused by mutations in the *NLRP3* gene encoding cryopyrin, characterized by excessive interleukin (IL)-1β secretion with subsequent local or systemic inflammation. We report here a case of a 9-year-old boy with a heterozygous mutation in the *NLRP3* gene who was diagnosed with CAPS. The patient's mother and 2 sisters had the same mutation.

CASE REPORT

A 9-year-old boy had recurrent skin eruptions associated with fever and arthralgia, which were exacerbated by cold exposure. The skin rash developed immediately after birth and was not improved by antihistamines and topical steroids. Physical examination revealed numerous small erythematous papules, plaques and purpura distributed on the upper and lower extremities (**Fig. 1**A and B). These skin lesions were painful, but not accompanied by itching, and persisted for 48–72 h. The patient also had a low-grade fever, polyarthralgia, headache, and hearing loss. Haematological examination revealed that the white blood cell count and C-reactive protein (CRP) level were within normal limits. His erythrocyte sedimentation rate (ESR) was elevated (27.4 mm/h). His serum amyloid A level was not elevated. Levels of rheumatoid factor, anti-nuclear antibody, complement, and serum and urine protein were all unremarkable. The patient was negative for anti-myeloperoxidase–anti-neutrophil cytoplasmic antibody (MPO-ANCA), anti-proteinase 3-anti-neutrophil cytoplasmic antibody (PR3-ANCA), and cryoglobulin. Serum IL-1β level, measured by enzyme-linked immunosorbent assay (ELISA), was 23.0 pg/ml. Serum IL-23 level was markedly elevated (1,442 pg/ml). Histopathological examination of a biopsy specimen from the lower leg revealed dermal perivascular infiltration of many inflammatory cells. Mild interstitial infiltrate was also seen throughout the dermis (Fig. 1C). Many inflammatory cells composed of lymphocytes, neutrophils with leukocytoclasia, histiocytes and eosinophils were detected around the vessels. Extravasation of red blood cells was observed. Fibrin deposition on the vessels was not apparent (Fig. 1D). On direct immunofluorescence analysis, only linear staining for IgM on the basement membrane zone was detected; no staining for IgG, IgA or C3 was observed. The patient's 2 sisters, mother and maternal grandmother also had histories of similar urticarial-like rashes (**Fig. 2**A and B), periodic fever and arthralgia, which were exacerbated by cold. The family pedigree indicated autosomal dominant inheritance of the condition (**Fig. 3**A). Due to these clinical and histological findings and family history, CAPS was suspected and genetic analysis was performed. A heterozygous missense mutation (c.1322C>T, p.A441V) at exon 3 of *NLRP3* was detected in the genomic DNA by direct sequencing (Fig. 3B). The patient's mother and 2 sisters had the same mutation. The patient was treated with the non-steroidal anti-

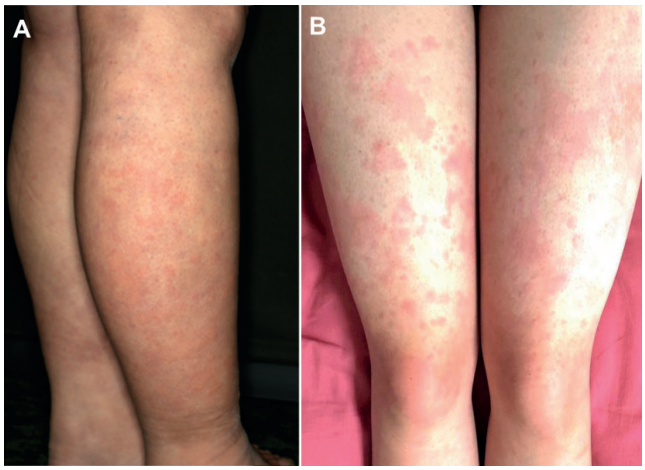

Fig. 2. (A) Urticaria-like erythematous lesions were detected on the lower extremities of the patient's mother. There were no purpuric lesions. (B) The patient's sister presented with urticaria-like eruptions on the lower extremities.

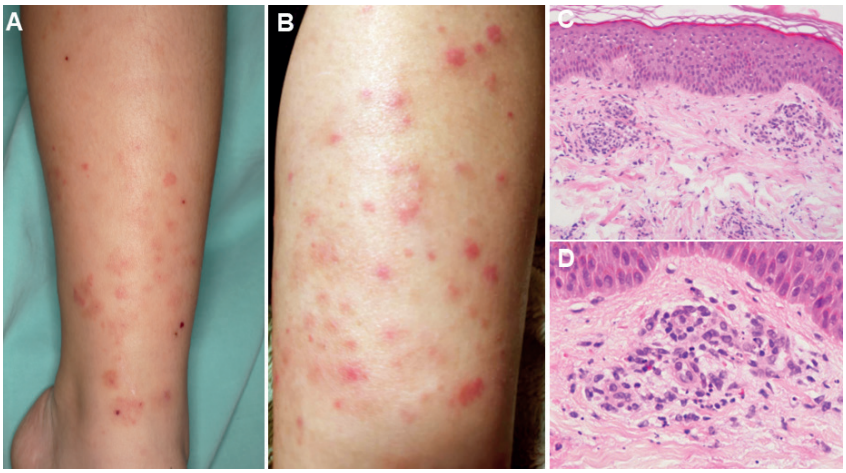

Fig. 1. (A) Numerous small erythematous papules and plaques were present on the lower extremities. (B) Purpuric lesions were detected on the lower extremities. (C) The biopsy specimen showed dermal perivascular infiltration of many inflammatory cells. Mild interstitial infiltration was also observed throughout the dermis. Haematoxylin and eosin staining (original magnification ×100). (D) Many inflammatory cells composed of lymphocytes, neutrophils with leukocytoclasia, histiocytes and eosinophils were detected around the vessels. Extravasation of red blood cells was also observed. Fibrin deposition on the vessels was not apparent. Haematoxylin and eosin staining (original magnification ×400).

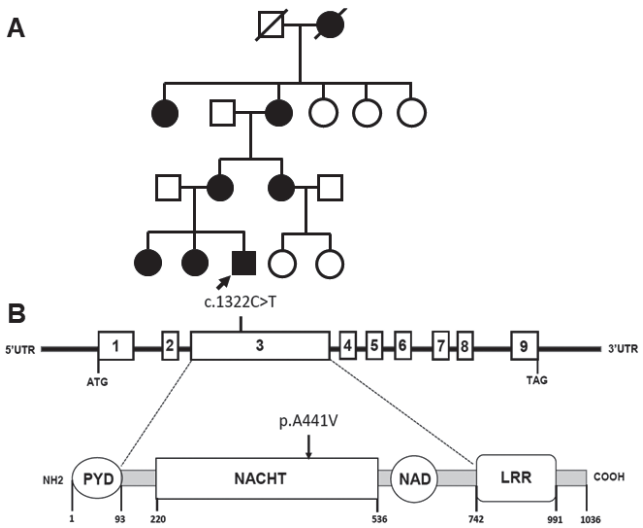

Fig. 3. (A) Family pedigree of the patient. ●, affected female; ■, affected male; ○, unaffected female; □, unaffected male. (B) Exonic organization of the human NLRP3 cDNA and domain organization model of the corresponding protein. A heterozygous missense mutation (c.1322C>T, p.A441V) at exon 3 of NLRP3 was detected in the genomic DNA by direct sequencing. NACHT: NAIP, CIITA, HET-E and TP1 domain; NAD: NACHT-associated domain; LRR: leucine-rich repeat domain; PYD: pyrin domain.

inflammatory drug (NSAID) loxoprofen sodium hydrate, at a dose of 60 mg twice daily, which subjectively reduced the severity of skin lesions. We are currently in the process of obtaining approval for IL1-antagonist treatment and getting consent from the family.

DISCUSSION

CAPS is a rare autoinflammatory syndrome with autosomal dominant inheritance, caused by mutations in the *NLRP3* gene encoding cryopyrin (1). Continuous NLRP3 activation results in excessive IL-1β secretion, which induces severe inflammation, seen as urticaria-like rash, fever and arthralgia (1, 2). CAPS has 3 clinical phenotypes: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA) (1–4). In the reported case, the age of disease onset in the family members ranged between 0 and 3 years. All of them presented with urticaria-like skin lesions, triggered by cold. The skin eruptions did not resolve within 24 h; they persisted for 48–72 h. The skin lesions were induced by not only cold exposure, but also other factors, such as exercise, stress and fatigue, which is not typical of FCAS. The patient had low-grade fever, polyarthralgia, headache, and hearing loss. We suspected that this patient had overlapping FCAS and MWS.

CAPS is usually caused by mutations concentrated in exons 3, 4 and 6 of *NLRP3*, and primarily in exon 3 encoding the NAIP, CIITA, HET-E and TP1 (NACHT) domain (5). In the present case, a heterozygous p.A441V mutation was detected in exon 3 of *NLRP3* encoding the NACHT domain. To our knowledge, this is the third family in which this rare mutation has been reported (6). The previous reports were in a multigenerational French family with MWS and a patient originating from Portugal with FCAS (6). The pathogenic and functional importance of this mutation was investigated by Awad et al. (6). HEK293T cells, transiently expressing the mutated NLRP3 (NLRP3-A441V), increased ASC speck formation, and the levels of IL-1β secreted by transfected THP-1 cells were significantly higher compared with controls. In addition, inflammasome-related gene expression and cytokine secretion by monocytes isolated from these patients was elevated compared with controls. These findings demonstrated the pathogenic role of the p.A441V missense mutation in families with CAPS.

The urticarial rash is the most common skin lesion in patients with CAPS, although the current patient presented not only with erythematous lesions, but also with purpuric lesions and severe pain. Histologically, no fibrin deposition on the vessels was apparent, but extravasation of red blood cells and perivascular infiltrate of many neutrophils with leukocytoclasia were observed. Urticarial vasculitis or ANCA-associated vasculitis should also be included in the differential diagnosis according to these clinical and histological findings in the current case. The patient was negative for MPO-ANCA, PR3-ANCA and cryoglobulin, and no staining for IgG, IgA, IgM or C3 on the walls of the vessels was detected by direct immunofluorescence analysis. The mechanism of these purpuric eruptions is unclear. Severe inflammation or certain inflammatory cytokines may have a strong influence on blood vessels. Other factors, such as underlying disease, age, individual characteristics and inducing factors, may also be associated with these clinical findings. Interestingly, the patient's mother and 2 sisters presented mainly with urticaria-like lesions and showed no purpuric lesions (Fig. 2A and B).

Continuous IL-1β secretion due to NRLP3 mutation is thought to be a fundamental cause of CAPS symptoms. However, the serum IL-1β level is not always elevated because of its short half-life in the patient's serum. In this case, the patient's serum IL-1β level, measured by enzyme-linked immunoassay (ELISA), was elevated. In addition, his serum IL-23 level markedly exceeded the normal range. Previous reports suggest that exaggerated IL-1β secretion due to *NLRP3* mutations affects the IL-23/IL-17 axis and plays an important role in T helper cell-17 differentiation in patients with CAPS (7, 8). Nevertheless, the important role of IL-23 in the development of CAPS has not been discussed previously. These serum cytokine levels (IL-1β and IL-23) may be useful for the evaluation of disease activity or treatment effectiveness in patients with CAPS.

In conclusion, dermatologists should consider CAPS as a differential diagnosis in cases with recurrent urticaria-like or purpuric eruptions appearing immediately after birth. Genetic analysis of the *NLRP3* gene is essential, and enables early diagnosis.

The authors have no conflicts of interest to declare.

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