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Case Report

Recurrent sterile arthritis with co-mutations of *PSTPIP1* and *MEFV* in girl

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Abstract

A 3-year-old girl with recurrent sterile arthritis and was found to have mutations of both *PSTPIP1* and *MEFV*, genes responsible for pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome, and familial Mediterranean fever, respectively. Cytokine profiling revealed high levels of IL-1β but not IL-6 in the synovial fluid. Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome is an autosomal dominant, rare autoinflammatory disorder characterized by destructive inflammation of the joints. Familial Mediterranean fever is characterized by recurrent fever, abdominal pain, synovitis, and pleurisy, and is correlated with abnormalities in the signaling pathway of inflammasomes. Cytokine profiling revealed inflammasome activation in the patient's joints.

Introduction

Recently, the genes responsible for chronic arthritis have been elucidated and the new disease concept of autoinflammatory disorders established. Familial Mediterranean fever (FMF) caused by mutation of *MEFV*, a representative autoinflammatory disease, is sometimes accompanied by arthritis. Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome (PAPA) is an autosomal dominant, rare, and relatively new autoinflammatory disorder characterized by destructive inflammation of the skin and joints. It is caused by mutation of the proline serine threonine phosphatase-interacting (*PSTPIP1*) gene on chromosome 15q[1)2)]. Here, we report a 3-year-old girl with recurrent sterile arthritis who was found to have mutations of both *PSTPIP1* and *MEFV*, which are responsible for PAPA and FMF[3)], respectively.

Case

The patient was a 3-year-old girl who was referred to our hospital in October 2012 due to fever and pain arising from coxitis in her left hip. Her neonatal (40 weeks and 2 days, 3,308 g) and past histories were unremarkable. Her family history was as follows : her younger sister had patent ductus arteriosus and her father had complained of arthralgia of unknown origin several times since his youth.

The patient developed arthralgia in the left knee joint in the middle of October. After a few days, the arthralgia disappeared spontaneously. On October 31, she developed a fever and arthralgia in the left knee and hip joint, making walking difficult. On admission, her body temperature was 38.2°C, her blood pressure 110/81 mmHg, and heart rate 120/min. Her bulbar conjunctiva was not injected. Her palpebral conjunctiva was not anemic. Her throat, breathing, and heart sounds were normal. There was no lymphadenopathy or hepato-

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splenomegaly. The range of movement in the left hip joint was limited due to pain.

The white blood cell count was 11,800/μL (neutrophils 72.6%, lymphocytes 17.3%, basophils 0.0%, eosinophils 0.4%, monocytes 9.7%). The hemoglobulin value was 12.8 g/dL. The platelet count was 726×10^3/μL. Her aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltranspeptidase levels were 25 IU/L, 11 IU/L, and 8 IU/L, respectively. The total and direct bilirubin levels were 0.65 mg/dL and 0.04 mg/dL, respectively. Her alkaline phosphatase level was 59 U/L. The serum amylase concentration increased to 71 U/L. The results of kidney function tests and urinalysis were normal. The erythrocyte sedimentation rate was 27 mm/hr. The blood clotting time and fibrin degradation product level were normal. The C-reactive protein level was high, at 0.9 mg/dL. The IgG, IgA, and IgM values were 889 mg/dL, 71 mg/dL, and 97 mg/dL, respectively. Her serum amyloid A level was high, at 875 (<8) μg/mL. Her ferritin level was 25.9 ng/mL. The levels of matrix metalloptpteinase-3, rheumatoid factor, procalcitonin, anti-nuclear antibody, and antistreptolysin-O were normal or below detectable levels.

The patient was admitted 4 times due to arthralgia in the bilateral hip joints (Fig. 1). Each time, her pain and fever spontaneously disappeared with antibiotic treatment. However, the synovial fluid culture was sterile.

Gallium scintigraphy revealed inconsiderable uptake in the bilateral hip, shoulder, knee, and ankle joints without changes on X-ray, which were judged as normal. An MRI revealed trapped synovial fluid in the left coxa. The patient showed periodic fever and sterile arthritis.

Subsequently, genomic studies revealed that she had heterozygous c.250G>A (p.E84K) of *MEFV* and heterozygous c.1106A>G (p.D369G) of *PSTPIP1*. No mutation was observed of *NLRP3*. Prednisolone was administered on demand under diagnosis of PAPA with/without FMF, and her arthritis was well controlled for 2 years.

The levels of 3 chemokines and 14 other cytokines were measured using a Bio-Plex suspension array (Bio-Rad Laboratories, Tokyo, Japan) or 17-Plex Panel (Bio-Rad Laboratories). Cytokine profiling revealed increased levels of IL-1β, IL-8, and TNF-α in the synovial fluid. However, her serum IL-1β and IL-8 levels were below detectable levels during the acute phases (Fig. 2).

Discussion

Autoinflammatory diseases are characterized by periodic fever or inflammation without infection or autoimmunity. First reported in 1997[2], PAPA is characterized by pyogenic arthritis, pyoderma gangrenosum, and severe cystic acne. Ten affected family members manifested variable expression of pauciarticular, nonaxial,

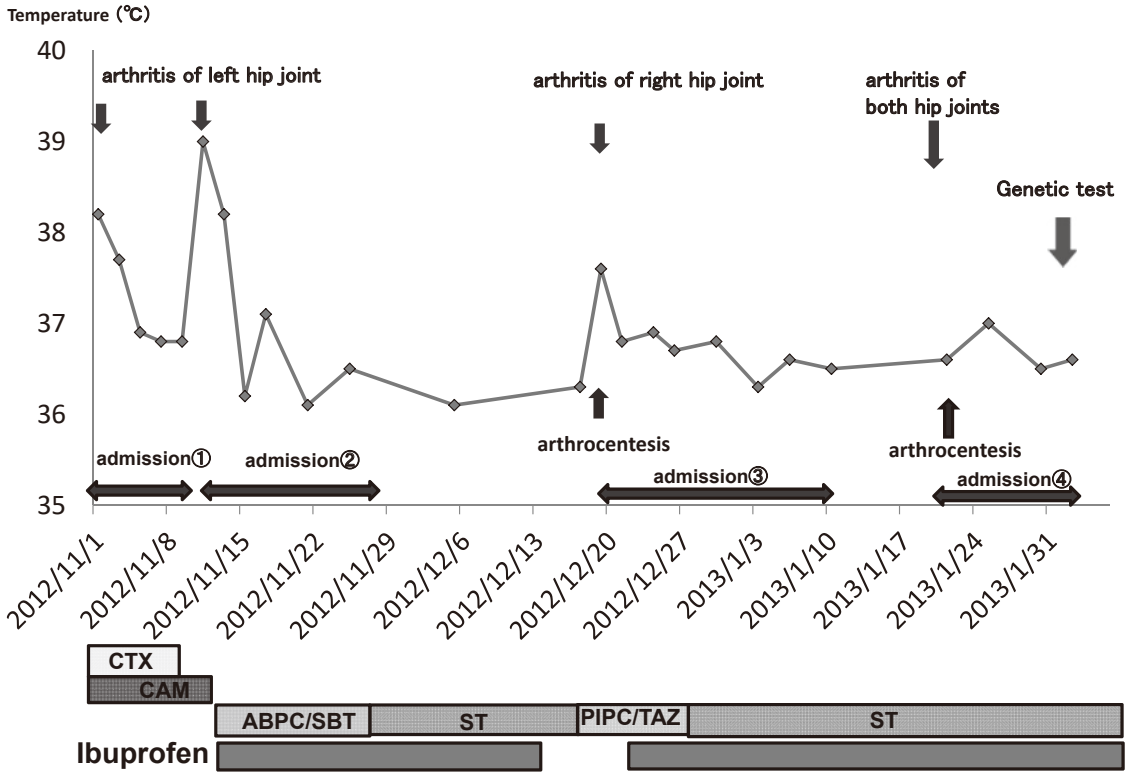

Fig. 1 Clinical course of patient (CTX : cefotaxime, CAM : clarithromycin, ABPC : ampicillin, TAZ : tazobactam, ST : sulfamethoxazole-trimethoprim, PIPC : piperacillin)

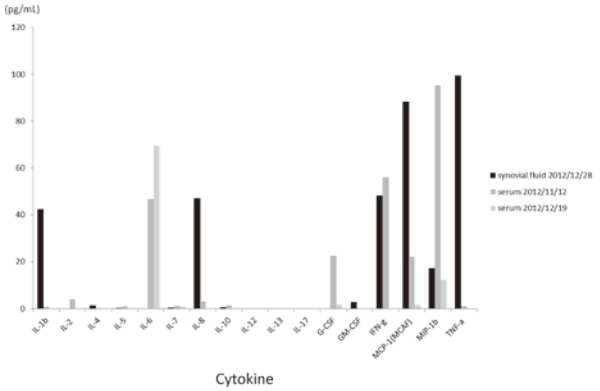

Fig. 2 Cytokine profiling (pg/mL) in serum (acute phases) and synovial fluid

destructive, corticosteroid-responsive arthritis commencing in childhood ; pyoderma gangrenosum ; and severe cystic acne in adolescence. Mutation of *PSTPIP1* is responsible for intractable arthritis[1)4)]. Also a common autoinflammatory disease, FMF is characterized by recurrent fever, abdominal and chest pain, and arthritis, and is a hereditary disorder caused by mutation of *MEFV*[5)6)].

Identification of the mutated gene is important in diagnosing and determining the pathophysiology of autoinflammatory diseases[7)]. The present patient had a heterozygous mutation of both *MEFV* and *PSTPIP1*. Only 4 cases with PAPA have been reported thus far in Japan (Table 1)[8-11)]. The patient in the present case report had neither skin infections nor a family history of pyoderma gangrenosum. The protein PSTPIP1 binds to pyrin. Mutation of the gene is speculated to enhance binding, eventually reducing its anti-inflammatory effect[12)].

In an earlier study by another group, genomic data from 26 Japanese children with FMF were analyzed and the responsiveness of the children to colchicine investigated. Typical FMF was diagnosed in 8 children from 6 families. The remaining 20 patients had no significant *MEFV* mutations. Conversely, patients with *MEFV* mutations were unresponsive in all cases. This suggested that other genomic candidates or abnormal epigenetic modifications were likely associated with FMF[13)], including *PSTPIP1*. Some clinical similarities are observed between FMA and PAPA, including a neutrophil-rich sterile joint infiltrate[4)]. The present patient had an E84K mutation of *MEFV* and D369G mutation of *PSTPIP1*. E84K in exon 1 of *MEFV* has been recognized in 2.4% of Japanese FMF patients. However, E84K has also been recognized in 1.3% of healthy Japanese subjects[14)]. D369G in *PSTPIP1* is a newly recognized mutation, although A230T, E250Q, and E250K have been reported in PAPA syndrome patients[1)4)].

Pyrin, which is mutated in FMF, is able to interact with crucial elements of NOD-like-receptor family pyrin domain containing 3 (NLRP3) inflammasomes, such as ASC and caspase 1, and it has been postulated that pyrin mutations could induce a loss of function in its potential inhibitory action on the NLRP3 inflammasome[15)16)]. NLRP3 finally induces the process of IL-1β activation through caspase 1. Cytokine profiling in the present study revealed high levels of IL-1β but not IL-6 only in synovial fluid, indicating inflammasome activation in the joints[17)]. Mutation of both *MEFV* and *PSTPIP1* might enhance inflammasome activation. Shoham et al. reported that PSTPIP1, a tyrosine-phosphorylated protein involved in cytoskeletal organization, also interacts with pyrin by *in vitro* examination of a coexpressed cell line. They hypothesized that PAPA-associated *PSTPIP1* mutations exert a dominant-negative effect on pyrin activity[18)]. More studies are needed to clarify this effect by investigating patients with periodic fever and arthritis.

Table 1 Profile of reported cases with PAPA in Japan

		Case 1 (0hno[8)])	Case 2 (Saito[9)])	Case 3 (Watabe[10)])	Case 4 (Ichida[11)])	Current patient
age at diagnosis (years)		3	21	30	16	3
gender		female	male	female	female	female
age at first symptoms (years)	arthritis	infant	6	6	3	3
	pyoderma gangrenosum or severe acne	15	20	13	3	none
	ulcer	none	6	infant	3	none
	other symptoms	15 (abdominal pain and diarrhea)	none	16 (edema of extremities and face)	31 (subarachnoid hemorrhage)	none
genomic study		not written	*CD2BP1*	*PSTPIP1* (normal)	*PSTPIP1* (G258A)	*PSTPIP1* (A84G) *MEMV* (G84L)

Conflict of interest (COI)

This work was not supported by a grant, and there is no conflict with any employment. Informed consent was obtained from the family involved in this study for publication.

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PSTPIP1 と *MEFV* 遺伝子変異を伴った再発性無菌性関節炎の一女児例

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【要旨】 再発性無菌性関節炎の 3 歳の女児例を経験した。精査にて PAPA 症候群と家族性地中海熱の責任遺伝子である *PSTPIP1* と *MEFV* に変異を伴っていた。精査にて関節液では IL-1β と IL-8 の上昇を認めていた。PAPA 症候群は常染色体優性遺伝の稀な自己炎症性疾患の一つで、破壊性の関節炎を主体とする。一方、家族性地中海熱は再発性発熱と腹痛、漿膜炎、胸膜炎を主症状とする疾患であり、インフラマゾームのシグナル伝達の異常によると考えられている。患児での関節液のサイトカインプロファイリングは、インフラマゾーム活性化に合致し、病態との関連が示唆された。

〈キーワード〉 arthritis、PAPA、*MEFV*、*PSTPIP1*、家族性地中海熱