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Immunoglobulin A Vasculitis in a Japanese Patient with Complete Familial Mediterranean Fever Carrying *MEFV* Exon 10 Mutation

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Immunoglobulin A (IgA) vasculitis is a systemic small-vessel vasculitis involving the skin, kidney, joints, and gastrointestinal tract. Familial Mediterranean fever (FMF) is the most common autoinflammatory disease characterized by periodic fever, peritonitis, pleuritis, or arthritis. It is well known that FMF may coexist with vasculitis, especially small and medium vessel vasculitis. Here we present a Japanese male patient with FMF who later developed IgA vasculitis and a relapsing disease course. A 51-year-old Japanese male was referred because of upper abdominal pain, arthralgia, and bilateral purpura of the lower limbs. He fulfilled the criteria for IgA vasculitis, which was successfully treated by corticosteroid and immunosuppressive therapy. He had a medical history of periodic fever since the age of 10 years old. The Mediterranean fever (*MEFV*) gene analysis revealed that he was heterozygous for M694I and E148Q mutations. Colchicine therapy resolved his periodic febrile attacks. To our knowledge, coexistence of FMF with IgA vasculitis has not been reported in East Asia, including Japan. Our case suggests that *MEFV* gene exon 10 mutations could be related to the development of IgA vasculitis and affects its clinical course.

Keywords: autoinflammatory disease; familial Mediterranean fever; fever of unknown origin; IgA vasculitis; MEFV gene
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Introduction

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease (Onen 2006). Immunoglobulin A (IgA) vasculitis is characterized by deposition of IgA-containing immune complexes in the walls of small vessels (Audemard-Verger et al. 2015). The co-occurrence of FMF and vasculitis was widely reported in the Mediterranean population (Abbara et al. 2019). Among vasculitis, IgA vasculitis, periarteritis nodosa (PAN), and Behçet's disease (BD) were considered to be three of the most prevalent vasculitis in patients with FMF (Abbara et al. 2019). However, the coexistence of FMF and IgA vasculitis has not been described in East Asian populations, including Japan. In light of a recently conceptualized continuum between autoimmune and autoinflammatory diseases, it is possible that the alternations of innate immunity may partly contribute to the pathophysiological processes of IgA vasculitis (Park et al. 2012). Also, mutations in the Mediterranean fever (*MEFV*) gene seem to play an important role in the progression of this rare association. Abnormalities of the *MEFV* gene have been suggested as involved in the exacerbation of inflammatory responses in IgA vasculitis (Aksu and Keser 2011). Here we report a case of periodic fever with recurrence of IgA vasculitis 10 years after the first onset of IgA vasculitis. The relapsing IgA vasculitis was resolved by corticosteroid and immunosuppressive therapy. Genetic analysis using autoinflammatory disease panel revealed compound heterozygous mutations of E148Q and M694I of *MEFV* gene, leading to the diagnosis of complete FMF.

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Case Presentation

A 51-year-old Japanese man was referred to our hospital for strong upper abdominal pain, diarrhea, arthralgia, and bilateral leg purpura. His past medical history included IgA vasculitis. The diagnosis of IgA vasculitis was based on the presence of fever, palpable purpura, proteinuria, and typical pathological findings of skin biopsy conducted 15 years ago. He was treated with corticosteroid for one year. Because the disease activity of IgA vasculitis was in remission, corticosteroid therapy was stopped 13 years ago. He had a 40-year history of recurrent chest pain and fever, which resolved within two days. He had not seen the hospital because his symptoms improved within a few days. His family history revealed that his mother also had recurrent fever and chest pain monthly. His life and allergy histories were unremarkable.

His vital signs on admission were as follows: the body temperature was 36.7℃, the blood pressure 164/98 mmHg, the pulse rate 55 beats/min and regular, and the oxygen saturation (SpO_2) 98% while he was breathing ambient air. Chest examination was unremarkable. Abdominal examination revealed upper abdominal tenderness. Purpura and pitting edema were observed in bilateral legs. Results of peripheral blood cell counts and serum biochemistries are described in Table 1. Laboratory findings showed leukocytosis (11,800 /μL) and elevated C-reactive protein levels (9.04 mg/dL). Markers for autoimmune diseases, including anti-nuclear antibody and anti-neutrophil cytoplasmic antibody, were negative. Serological testing was negative for hepatitis C virus, human immunodeficiency virus, and syphilis. Although hepatitis B surface (HBs)-antibody and hepatitis B core (HBc)-antibody were positive, hepatitis B virus-deoxynucleic acid (HBV-DNA) testing was negative. Coagulation factor XIII activation was decreased to 37% (reference range, 70%-140%). Dipstick urinalysis showed protein ± and blood 1+.

Enhanced abdominal computed tomography (CT) images showed wall thickening of ileocecum and terminal ileum with a small amount of ascites fluid (Fig. 1A, B). Endogastroduodenoscopy only revealed fundi gland polyp in duodenum. He was diagnosed as having recurrent IgA vasculitis because he fulfilled the American College of Rheumatology 1990 criteria for the classification of

Table 1. Laboratory findings on the first admission.

Peripheral blood		**Serological tests**	
Red blood cells	573 × 10^4/μL	C-reactive protein	9.04 mg/dL (< 0.14)
Hemoglobin	14.5 g/dL	IgG	1,136 mg/dL (861-1,747)
Hematocrit	42.7%	IgA	398 mg/dL (93- 393)
Platelets	295,000/μL	IgM	170 mg/dL (33-183)
White blood cells	11,800/μL	ANA	< 40 (< × 40)
Neutrophil	89.2%	Anti-ds-DNA Ab	2.8 (< 9.9)
Eosinophil	0.4%	PR3-ANCA	(−) (< 2.0 U/mL)
Monocyte	3.8%	MPO-ANCA	(−) (< 3.5 U/mL)
Lymphocyte	6.5%	HBs-Ag	(−)
Basophil	0.1%	HBs-Ab	(+)
Blood chemistry		HBc-Ab	(+)
Total protein	6.4 g/dL	HBV-DNA	(−)
Total bilirubin	0.56 mg/dL	HCV-Ab	(−)
Albumin	3.1 g/dL	PT	84.4% (80-100)
Asparate transaminase	21 IU/L (13-30)	PT-INR	1.09 (1.0-1.08)
Alanine transaminase	24 IU/L (10-42)	APTT	30.7 (25-38)
Lactate dehydrogenase	190 IU/L (12-222)	D-dimer	27.6 μg/mL (0-1)
Alkaline phosphatase	225 IU/L (106-322)	F13	37 (70-140)
Creatine Kinase	98 IU/L (59-248)		61.4 (70-140)
Blood urea nitrogen	20 mg/dL (8.0-20.0)	**Urinarysis**	
Creatinine	0.64 mg/dL (0.65-1.07)	Blood	(1+)
Sodium	139.3 mEq/L (138-145)	Protein	(−)
Potassium	3.73 mEq/L (3.6-4.8)		
Chloride	101.5 mEq/L (101-108)		

ANA, anti-nuclear antibody; Anti-dsDNA Ab, anti-double stranded DNA antibody; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; HBsAg, hepatitis B virus surface antigen; HBs-Ab, anti-hepatitis B virus surface antibody; HBc-Ab, anti-hepatitis B virus core antibody; HCV-Ab, hepatitis C virus antibody; PT, prothrombin; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; F13, Factor 13.

Henoch-Schönlein purpura based on palpable purpura and bowel angina. The decreased plasma levels of coagulation factor XIII activity supported the diagnosis of IgA vasculitis. He was treated with 40 mg/day of intravenous prednisolone following pulsed methylprednisolone therapy (1,000 mg/day for three consecutive days per week) (Fig. 2). All

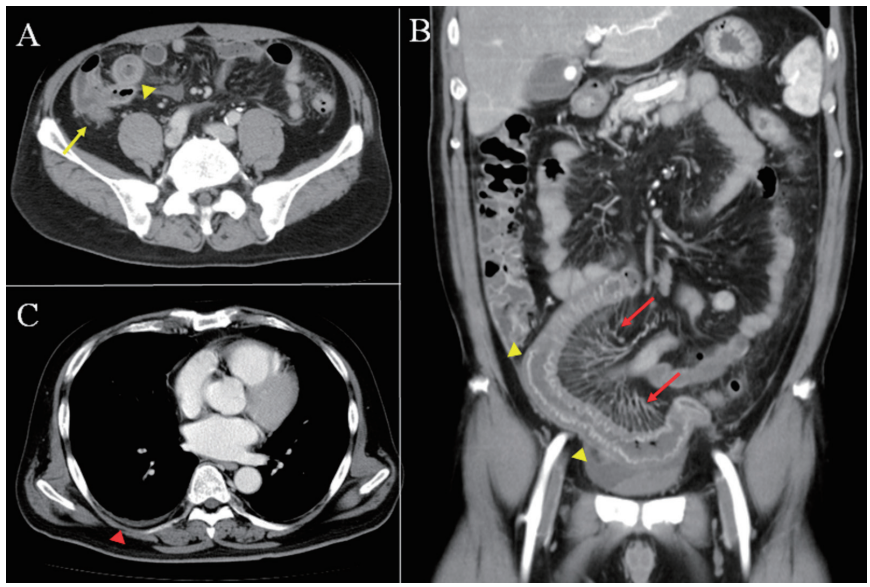

Fig. 1. Contrast-enhanced computed tomography (CT) findings.
(A) Enhanced abdominal CT images on the first admission showed wall thickening of ileocecum (yellow arrowhead) and terminal ileum (yellow arrow) with a small amount of ascites fluid.
(B) Enhanced abdominal CT images on the first admission. Coronal reformation showed wall thickening of ileocecum (yellow arrowheads) and pronounced hyper-attenuation of the mesenteric fat (red arrows).
(C) Chest axial CT finding two months after the second admission shows pleural thickening and pleural effusion in right lung (red arrowhead). The finding suggests the pleurisy.

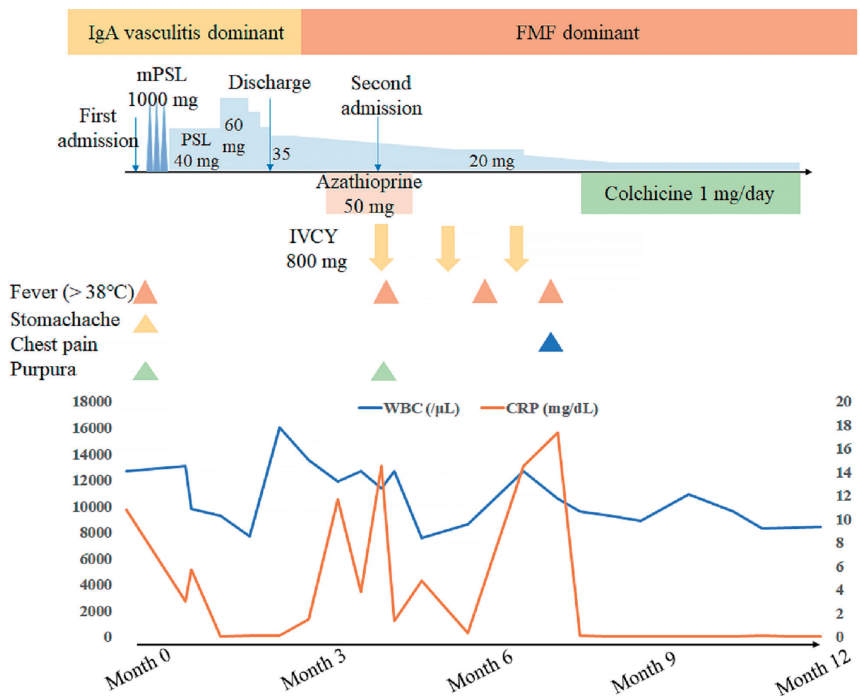

Fig. 2. The clinical course of a 51-year-old male Japanese patient with periodic fever.
After the administration of colchicine, his periodic symptoms and laboratory findings gradually improved.
CRP, C-reactive protein; mPSL, methylprednisolone; PSL, prednisolone; IVCY, intravenous cyclophosphamide pulse therapy; WBC, white blood cell count.

symptoms disappeared after treatment. However, the C-reactive protein (CRP) levels were elevated to 4.44 mg/dL two weeks after treatment. Therefore, the amount of oral prednisolone was increased to 60 mg/day. Because the laboratory result showed improved CRP, he was discharged from our hospital with 35 mg/day of oral prednisolone at 60 days after admission.

Two months after the first admission, a few palpable purpuras occurred to bilateral legs and the CRP levels were elevated to 11.72 mg/dL (Fig. 2). Oral azathioprine (50 mg/day) was added because of the exacerbation of IgA vasculitis and his symptoms improved temporarily. Three months after first admission, he was readmitted for intravenous cyclophosphamide pulse therapy (IVCY, 500 mg/body). At five days after the second admission, he had fever, slight epigastralgia, and elevated CRP levels (19.89 mg/dL). Fever workup such as blood test, urine test, blood cultures, chest and abdominal X-ray was not significant except elevated CRP levels. Although infection was not suspected, antibiotics was administered because of strong inflammation. His symptoms improved within a few days, but he was hospitalized for two weeks because of prolonged inflammation shown by blood test results. Although he continued to receive monthly IVCY treatment, his symptoms such as fever and slight abdominal pain were repeated every two months. He had chest pain two months after the second admission. Chest CT findings showed pleural thickening and pleural effusion in the right lung (Fig. 1C). A diagnosis of FMF was also suspected based on the presence of periodic fever and pleuritis. Therefore, written informed consent for gene analysis for autoinflammatory genes was obtained from the patient. This analysis showed a compound heterozygous for E148Q and M694I mutations of MEFV. The mutation of MEFV exon 10, including M694I, is generally associated to a typical FMF phenotype. He also fulfilled Tel-Hashomer criteria for FMF with typical attacks such as generalized peritonitis, unilateral pleuritis and fever alone within 3 days (Livneh et al. 1997). He started colchicine therapy for FMF and all his symptoms disappeared (Fig. 2). His condition significantly improved on follow-up, suggesting that the overlapping FMF had also subsided because of the colchicine therapy.

Informed consent was obtained from the patient. Because of a case report of single patient, ethical approval was waived for institutional review board in Fukushima Medical University.

Discussion

IgA vasculitis is an IgA immune complex-mediated small-vessel vasculitis of the skin, bowel, joints, and kidneys (Audemard-Verger et al. 2015). It is clinically characterized by non-thrombocytopenic purpura, abdominal pain, and arthralgia or arthritis (Audemard-Verger et al. 2015). The exact cause is unknown; however, both genetic and environmental factors are thought to play a role in its development (Heineke et al. 2017). FMF is a monogenic autoinflammatory disease characterized by periodic fever and polyserositis (Onen 2006). FMF is not a rare disease in Japan (Migita et al. 2016); however, no associations between IgA vasculitis and FMF with exon 10 variants have been reported in East Asia, including Japan. This is the first case report of IgA vasculitis in a Japanese patient with complete FMF carrying *MEFV* exon 10 mutation. The complication of both IgA vasculitis and FMF also has not been reported in Japanese patients with other mutations of *MEFV* gene. Several investigations reported increased frequencies of IgA vasculitis in patients with FMF in a Mediterranean population (Abbara et al. 2019; Atas et al. 2020). Furthermore, several studies suggested associations between *MEFV* mutations and the susceptibility or outcome of IgA vasculitis (Ekinci et al. 2019; Cakici et al. 2019). In the system review, IgA vasculitis is the most prevalent vasculitis with a prevalence of 0.9%-1.4% in FMF patients, followed by PAN with a prevalence 0.9%-1.4% (Abbara et al. 2019; Balci-Peynircioglu et al. 2020). In most patients, FMF precede IgA vasculitis (Abbara et al. 2015, 2019). Abbara et al. (2015) reported that some FMF patients developed vasculitis in adulthood as well as our case. Furthermore, IgA vasculitis is not presumed to be a distinct entity in the presence of FMF, since its onset might be influenced by the presence of FMF and *MEFV* mutations (Abbara et al. 2019). FMF is caused by mutations in the *MEFV* gene, leading to pyrin-inflammasome activation and resulting in the activity of proinflammatory cytokines, especially interleukin (IL)-1β. It is unclear whether *MEFV* mutations are responsible for the coexistence of IgA vasculitis and FMF. However, recent studies have suggested that *MEFV* variants in exon 10 affect the clinical presentation of IgA vasculitis where FMF is endemic (Ozcakar et al. 2008; Cakici et al. 2019). *MEFV* mutations on exon 10 were found in 34% of 80 patients with IgA vasculitis. Age at diagnosis was younger, and presence of edema and elevated erythrocyte sedimentation rate and CRP were significantly higher in patients with *MEFV* exon 10 mutations (Ozcakar et al. 2008). Another study showed that 44% of patients had one of the *MEFV* mutations, and patients with IgA vasculitis and M694V mutations had higher CRP and serum IgA levels (Bayram et al. 2011). These studies suggest that *MEFV* mutations in exon 10 may affect the clinical manifestations of FMF. Alternations in the *MEFV* genes are important susceptibility factors for the development of IgA vasculitis and also affect the clinical presentations.

Although more than 20% of the Japanese population had E148Q variants (Sugiura et al. 2008), there are important findings which demonstrate that M694I mutation is a most penetrated mutation in Japanese patients with complete phenotype of FMF, which is rarely detected in healthy subjects (Migita et al. 2016). Therefore, the presence of *MEFV* exon 10 mutation as seen in the present study seems to be an important factor for the alternations of clinical phenotypes or course of IgA vasculitis in addition to the coexistence of FMF and IgA vasculitis. Pyrin plays a crucial

role in the inflammatory pathways of the innate immune system through the formation of pyrin-inflammasome (Schnappauf et al. 2019). A mutated pyrin secondary to *MEFV* exon 10 mutations seemingly augments inflammation secondary to the impaired regulatory system of pyrin-inflammasome (Jamilloux et al. 2018). This upregulated pyrin-inflammasome activation process may be a predisposition to chronic inflammatory diseases and vasculitis, including IgA vasculitis (Shin et al. 2019). Therefore, alternations in the *MEFV* gene exon 10 could be important susceptibility factors for the development of IgA vasculitis, as well as affect the severity of the clinical course of this disease.

Most *MEFV* carriers have subclinical inflammation (Lachmann et al. 2006). *MEFV* gene exon 10 mutations may upregulate innate immunity through pyrin-inflammasome activation and following IL-1β production (Ozen et al. 2017; Jamilloux et al. 2018). IL-18 is another inflammatory cytokine and contributes to the cytokine network in the inflammatory cascade of FMF (Haznedaroglu et al. 2005). Patients with FMF can be divided into two groups by concentration of IL-18 during the non-attack period: those with high IL-18 and those with low IL-18 (Wada et al. 2018). Subclinical inflammation persists in patients whose IL-18 does not decrease during the non-attack period (Wada et al. 2018). Furthermore, the serum levels of IL-18 in remission were significantly higher in the patients with *MEFV* mutation in exon 10 (Koga et al. 2016). On the other hand, the relation between IgA vasculitis and these inflammatory cytokines also has been reported. Urine levels of IL-1β were significantly higher in the IgA vasculitis with nephritis than IgA vasculitis without nephritis (Berthelot et al. 2018). The skin biopsy finding of IgA vasculitis in the acute phase revealed the positivity of IL-1 immunohistochemical staining in the nucleated epidermal layer (Besbas et al. 1997), and rs16944 genetic variant of IL-1β may be a genetic marker of severe renal manifestation of IgA vasculitis (Lopez-Mejias et al. 2016). Furthermore, serum or plasma levels of IL-18 were significantly higher in patients with IgA vasculitis than in controls and the activity of IgA vasculitis is associated with the titer of IL-18 (Wang et al. 2011; Mahajan et al. 2013). The imbalance of IL-18 and IL-18 binding protein, which is endogenous antagonist of IL-18, may promote inflammation in IgA vasculitis (Wang et al. 2011). The susceptibility to IgA vasculitis by specific IL-18 gene promoter polymorphisms was previously suggested (Torres et al. 2010). These findings suggest that *MEFV* gene exon 10 mutations affect the development of the clinical course of IgA vasculitis through the activation of innate immunity. Pathogenesis of IgA vasculitis mostly involves adaptive immune cell-mediated immunity (Heineke et al. 2017). However, innate immune activation might perpetuate adaptive and immune responses, as well as have an effect on the course of IgA vasculitis (Chang and Li 2020). Further studies are needed to elucidate whether *MEFV* exon 10 mutations provide a basis for the development of IgA vasculitis by forming a proinflammatory state in the Japanese population.

Our patient also showed a favorable response to corticosteroid plus immunosuppressive treatment; however, the course was unusual with relapsing IgA vasculitis 15 years after the initial onset. Even in non-FMF-endemic areas, *MEFV* gene analysis can be used to search for vasculitis patients with periodic fever. When vasculitis patients have recurrent FMF-related symptoms, even without serositis or synovitis, FMF should be considered as a differential diagnosis and *MEFV* gene analysis should be performed.

In conclusion, we report a Japanese patient with FMF and M694I mutation associated with IgA vasculitis. Although a clear association between the two disorders has not been established, the findings in this case suggest that FMF and IgA vasculitis may have the common pathophysiological processes, such as inflammasome activation, which may modulate the clinical course of IgA vasculitis. Further investigations are required to demonstrate whether this coexistence is due to a chance or a common pathogenic mechanism.

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Conflict of Interest

The authors declare no conflict of interest.

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