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発表者名	論文タイトル名	発表雑誌	巻号	ページ	出版年
Yokoyama K, Ikeya M, Umeda K, Oda H, Nodomi S, Nasu A, Matsumoto Y, Izawa K, Horigome K, Kusaka T, Tanaka T, Saito MK, Yasumi T, Nishikomori R, Ohara O, Nakayama N, Nakahata T, Heike T, Toguchida J.	Enhanced chondrogenesis of induced pluripotent stem cells from patients with neonatal-onset multisystem inflammatory disease occurs via the caspase 1-independent cAMP/Protein Kinase A/CREB pathway.	Arthritis Rheumatol	67	302-314	2015
Hirano M, Seguchi J, Yamamura M, Narita A, Okanobu H, Nishikomori R, Heike T, Hosokawa M, Morizane Y, Shiraga F.	Successful resolution of stromal keratitis and uveitis using canakinumab in a patient with chronic infantile neurologic, cutaneous, and articular syndrome: a case study.	J Ophthalmic Inflamm Infect.		印刷中	2015
Harada Y, Fukiage K, Nishikomori R, Suzuki S, Futami T.	CINCA syndrome with surgical intervention for valgus deformity and flexion contracture of the knee joint: A case report.	Mod Rheumatol.		印刷中	2015
Kido J, Mizukami T, Ohara O, Takada H, Yanai M .	Idiopathic disseminated bacillus Calmette-Guerin infection in three infants.	Pediatr Int.	57	750-3	2015
Kusuda T, Nakashima Y, Murata K, Kanno S, Nishio H, Saito M, Tanaka T, Yamamura K, Sakai Y, Takada H, Miyamoto T, Mizuno Y, Ouchi K, Waki K, Hara T.	*Kawasaki disease-specific molecules in* the sera are linked to microbe-associated molecular patterns in the biofilms.	PLoS One.		印刷中	2014
Nozawa T, Mori M, Nishimura K, Sakurai N, Kikuchi M, Hara R, Yokota S.	Usefulness of two IFN-γ release assays for patients with rheumatic disease.	Pediatr Int.		印刷中	2015
Yokota S, Itoh Y, Morio T, Sumitomo N, Daimaru K, Minota S.	Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis under Treatment with Tocilizumab.	J Rheumatol.	42	712-22	2015
Yokota S, Itoh Y, Morio T, Origasa H, Sumitomo N, Tomobe M, Tanaka K, Minota S.	Tocilizumab in systemic juvenile idiopathic arthritis in a real-world clinical setting: results from 1 year of postmarketing surveillance follow-up of 417 patients in Japan.	Ann Rheum Dis.		印刷中	2015
Yokota S, Kikuchi M, Nozawa T, Kanetaka T, Sato T, Yamazaki K, Sakurai N, Hara R, Mori M	Pathogenesis of systemic inflammatory diseases in childhood: "Lessons from clinical trials of anti-cytokine monoclonal antibodies for Kawasaki disease, systemic onset juvenile idiopathic arthritis, and cryopyrin-associated periodic fever syndrome".	Mod Rheumatol	25	1-10	2015
Ishikura K, Yoshikawa N, Nakazato H, Sasaki S, Nakanishi K, Matsuyama T, Ito S, Hamasaki Y, Yata N, Ando T, Iijima K, Honda M.	Japanese Study Group of Renal Disease in Children. Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial.	Pediatr Nephrol.	30	459-68	2015
Kobayashi I, Mori M, Yamaguchi K, Ito S, Iwata N, Masunaga K, Shimojo N, Ariga T, Okada K, Takei S.	Rheumatology Association of Japan recommendation for vaccination in pediatric rheumatic diseases.	Pediatric Mod Rheumatol.	25	335-43	2015
Takahashi T, Fujisawa T, Kimura M, Ohnishi H, Seishima M.	Familial Mediterranean fever variant with repeated atypical skin eruptions.	J Dermatol	42	903-905	2015
Takahashi T, Fujimoto N, Yamaguchi A, Hayashi H, Migita K, Ida H, Tanaka T.	Familial Mediterranean fever with onset in the 70s showing various neutrophilic dermatosis.	J Eur Acad Dermatol Venereol.		印刷中	2015
Yasunami M, Nakamura H, Agematsu K, Nakamura A, Yazaki M, Kishida D, Yachie A, Toma T, Masumoto J, Ida H, Koga T, Kawakami A, Eguchi K, Furukawa H, Nakamura T, Nakamura M, Migita K	Identification of disease-promoting HLA class I and protective class II modifiers in Japanese patients with Familial Mediterranean Fever.	PLoS One.	10	e0125938	2015
Yamazaki T, Shigemura T, Kobayashi N, Honda K, Yazaki M, Masumoto J, Migita K, Agematsu K	IL-18 serum concentration is markedly elevated in typical familial Mediterranean fever with M694I mutation	Mod Rheumatol		印刷中	2015
Migita K, Izumi Y, Fujikawa K, Agematsu K, Masumoto J, Jiuchi Y, Kozuru H, Nonaka F, Shimizu T, Nakamura T, Iwanaga N, Furukawa H, Yasunami M, Kawakami A, Eguchi K	Dysregulated mature IL-1beta production in familial Mediterranean fever.	Rheumatology		印刷中	2015
Yamagami K, Nakamura T, Nakamura R, Hanioka Y, Seki K, Chiba H, Kobayashi K, Agematsu K.	Familial Mediterranean fever with P369S/R408Q exon3 variant in pyrin presenting as symptoms of PFAPA.	Mod Rheumatol		印刷中	2015
Kawamura S, Agematsu K, Kawamura D, Kawamura G, Suzuki K, Minami M.	A Case Report of Familial Mediterranean Fever Diagnosed Following the Total Knee Arthroplasty.	HSS Journal	11	278-280	2015

Takahara T, Shimizu M, Nakagishi Y, Kinjo N, Yachie A	Serum IL-18 as a potential specific marker for differentiating systemic juvenile idiopathic arthritis from incomplete Kawasaki disease.	Rheumatol Int	35	81-84	2015
Shimizu M, Nakagishi Y, Inoue N, Mizuta M, Ko G, Saikawa Y, Kubota T, Yamasaki Y, Takei S, Yachie A.	Interleukin-18 for predicting the development of macrophage activation syndrome in systemic juvenile idiopathic arthritis.	Clin Immunol.	160	277-81	2015
Kawai T, Arai K, Harayama S, Nakazawa Y, Goto F, Maekawa T, Tamura E, Uchiyama T, Onodera M.	Severe and Rapid Progression in Very Early-Onset Chronic Granulomatous Disease-Associated Colitis.	J Clin Immunol.	35	583-8	2015
Nerome Y, Akaike H, Nonaka Y, Takezaki T, Kubota T, Yamato T, Yamasaki Y, Imanaka H, Kawano Y, Takei S.	The safety and effectiveness of HBV vaccination in patients with juvenile idiopathic arthritis controlled by treatment.	Mod Rheumatol		印刷中	2015
Yamasaki Y, Takei S, Imanaka H, Nerome Y, Kubota T, Nonaka Y, Akaike H, Takezaki T, Kawano Y.	Prediction of long-term remission of oligo/polyarticular juvenile idiopathic arthritis with S100A12 and vasucular endothelial growth factor.	Mod Rheumatol		印刷中	2015
Kubota T, Imanaka H, Takei S, Yamatou T, Nerome Y, Yamasaki Y, Nonaka Y, Akaike H, Takezaki T, Kawano Y.	Disease activity score in 28 joints at 3 months after the initiation of biologic agent can be a predictive target for switching to the second biologic agents in patients with polyarticular juvenile.	Mod Rheumatol		印刷中	2015
Kobayashi I, Mori M, Yamaguchi KI, Ito S, Iwata N, Masunaga K, Shimojo N, Ariga T, Okada K, Takei S.	Pediatric Rheumatology Association of Japan recemmendation for vaccination in pediatric rheumatic diseases.	Mod Rheumatol	25	335-343	2015
Umeda M, Aramaki T, Fujikawa K, Iwamoto N, Ichinose K, Terada K, Takeo G, Yonemitsu N, Ueki Y, Migita K, Kawakami A.	Tocilizumab is effective in a familial Mediterranean fever patient complicated with histologically proven recurrent fasciitis and myositis.	Int J Rheum Dis		印刷中	2015
Ashida M, Koike Y, Kuwatsuka S, Ichinose K, Migita K, Sano S, Utani A.	Psoriasis-like lesions in a patient with familial Mediterranean fever.	J Dermatol		印刷中	2015
Nonaka F, Migita K, Jiuchi Y, Shimizu T, Umeda M, Iwamoto N, Izumi Y, Mizokami A, Nakashima M, Ueki Y,	Increased prevalence of MEFV exon 10 variants in Japanese patients with adult-onset Still's disease.	Clin Exp Immunol	179	392-7	2015
Jo T, Horio K, Migita K.	Sweet's syndrome in patients with MDS and MEFV mutations.	N Engl J Med	372	686-8	2015
Migita K, Hisanaga S, Izumi Y, Kawahara C, Shigemitsu Y, Iwanaga N, Araki T, Kamata M, Izumi M, Kumagai K, Kawakami	Protracted arthritis in a Japanese patient with familial Mediterranean fever.	Mod Rheumatol	30	1-5	2015
Miyamae T, Tanaka E, Kishi T, Matsuyama T, Igarashi T, Fujikawa S, Taniguchi A, Momohara S, Yamanaka H	Long-term outcome of 114 adult JIA patients in a non-pediatric rheumatology institute in Japan.	Mod Rheumatol	25	62-66	2015
Kaji M, Kishi T, Miyamae T, Nagata S, Yamanaka H, and Fujikawa S.	Efficacy of Adalimumab in a Girl with Refractory Intestinal Behcet's Disease.	Case reports in rheumatology		716138	2015
Yanagi Y, Mizuochi T, Takaki Y, Eda K, Mitsuyama K, Ishimura M, Takada H, Shouval DS, Griffith AE, Snapper SB, Yamashita Y, Yamamoto K.	Novel exonic mutation inducing aberrant splicing in the IL10RA gene and resulting in infantile-onset inflammatory bowel disease: a case report	BMC Gastroenterology		in press	
Shimizu M, Hamaguchi Y, Ishikawa S, Ueno K, Yachie A.	Successful treatment with tocilizumab of a psoriasiform skin lesion induced by etanercept in a patient with juvenile idiopathic arthritis.	Mod Rheumatol	25 (6)	972-973	2015
Bousfiha A, Jeddane L, Al-Herz W, Ailal F, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, Etzioni A, Franco JL, Gaspar HB, Holland SM, Klein C,	The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies.	J Clin Immunol.	35(8)	727-738.	2015
Picard C, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, Etzioni A, Holland SM, Klein C, Nonoyama S, Ochs HD, Oksenhandler E, Puck JM, Sullivan KE, Tang ML, Franco JL, Boby Gaspar H.	Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015.	J Clin Immunol.		DOI 10.1007/s10875-015-0201-1.	2015
Fujimaru T, Ito S, Masuda H, Oana S, Kamei K, Ishiguro A, Kato H, Abe J	Decreased levels of inflammatory cytokines in immunoglobulin-resistant Kawasaki disease after plasma exchange.	Cytokine	70	156-60,	2014

III 研究成果の刊行物・別冊

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Enhanced Chondrogenesis of Induced Pluripotent Stem Cells From Patients With Neonatal-Onset Multisystem Inflammatory Disease Occurs via the Caspase 1–Independent cAMP/Protein Kinase A/CREB Pathway

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Objective. **Neonatal-onset multisystem inflammatory disease (NOMID) is a dominantly inherited autoinflammatory disease caused by NLRP3 mutations. NOMID pathophysiology is explained by the NLRP3 inflammasome, which produces interleukin-1β (IL-1β). However, epiphyseal overgrowth in NOMID is resistant to anti–IL-1 therapy and may therefore occur independently of the NLRP3 inflammasome. This study was undertaken to investigate the effect of mutated NLRP3 on chondrocytes using induced pluripotent stem cells (iPSCs) from patients with NOMID.**

Methods. **We established isogenic iPSCs with wild-type or mutant NLRP3 from 2 NOMID patients with NLRP3 somatic mosaicism. The iPSCs were differentiated into chondrocytes in vitro and in vivo. The phenotypes of chondrocytes with wild-type and mutant NLRP3 were compared, particularly the size of the chondrocyte tissue produced.**

Results. **Mutant iPSCs produced larger chondrocyte masses than wild-type iPSCs owing to glycosaminoglycan overproduction, which correlated with increased expression of the chondrocyte master regulator SOX9. In addition, in vivo transplantation of mutant cartilaginous pellets into immunodeficient mice caused disorganized endochondral ossification. Enhanced chondrogenesis was independent of caspase 1 and IL-1, and thus the NLRP3 inflammasome. Investigation of the human *SOX9* promoter in chondroprogenitor cells revealed that the CREB/ATF-binding site was critical for SOX9 overexpression caused by mutated NLRP3. This was supported by increased levels of cAMP and phosphorylated CREB in mutant chondroprogenitor cells.**

Conclusion. **Our findings indicate that the intrinsic hyperplastic capacity of NOMID chondrocytes is dependent on the cAMP/PKA/CREB pathway, independent of the NLRP3 inflammasome.**

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BRIEF REPORT Open Access

Successful resolution of stromal keratitis and uveitis using canakinumab in a patient with chronic infantile neurologic, cutaneous, and articular syndrome: a case study

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Abstract

Background: Cryopyrin-associated periodic syndrome (CAPS) is a group of rare autoinflammatory diseases, and of these, chronic infantile neurologic, cutaneous, and articular/neonatal-onset multisystem inflammatory disease (CINCA/NOMID) syndrome has the most severe phenotype. Canakinumab, a monoclonal antibody that targets interleukin-1β, has been shown to be an effective treatment for resolving systemic inflammation. However, its efficacy for treating ophthalmic symptoms of this disorder remains unclear.

Findings: A 64-year-old female reported episodes of nonpruritic urticaria, fever, aseptic meningitis, and bilateral sensorineural deafness. Her son had experienced similar symptoms. She was initially referred for ophthalmologic treatment for an infectious corneal ulcer. Examination of her right eye by slit lamp biomicroscopy showed diffuse conjunctival injection, corneal infiltrates, a corneal ulcer, and hypopyon. She was therefore treated aggressively with topical and systemic antibiotics in addition to antifungal medications. However, this was ineffective. Genetic analysis detected the heterozygous germline p.Asp303Asn mutation in the *NLRP3* gene in both our patient and her son. She was therefore diagnosed with CINCA/NOMID syndrome based on her clinical manifestations. All of the patient's physical and ophthalmic symptoms were resolved within a few days after the initiation of canakinumab treatment. During an 18-month follow-up period, no adverse events or severe infections were observed.

Conclusions: Our case report indicates that canakinumab is effective not only for the treatment of systemic inflammation but also for treating ophthalmic involvement, such as recurrent stromal keratitis and anterior uveitis.

Keywords: Cryopyrin-associated periodic syndrome, Chronic infantile neurologic, Cutaneous and articular/neonatal-onset multisystem inflammatory disease syndrome, Canakinumab, Stromal keratitis, Uveitis

Findings

Background

Cryopyrin-associated periodic syndrome (CAPS) is an autoinflammatory disorder caused by heterozygous mutations in the *NLRP3* gene and include three distinct conditions, namely familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurologic, cutaneous, and articular (also known as neonatal-onset multisystem inflammatory disease) (chronic infantile neurologic, cutaneous, and articular/neonatal-onset multisystem inflammatory disease (CINCA/NOMID)) syndrome [1–5]. Gain-of-function mutations in *NLRP3* result in the excessive production of the potent proinflammatory cytokine interleukin-1β (IL-1β), thereby evoking the autoinflammatory manifestations of CAPS [6–8]. CINCA/NOMID syndrome is the most severe

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PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Idiopathic disseminated bacillus Calmette–Guerin infection in three infants

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Abstract We describe the cases of three infants between 4 and 9 months of age with disseminated bacillus Calmette–Guerin (BCG) infection who developed persistent fever, skin rash, and multiple chest nodules visible on computed tomography 22–34 days after BCG vaccination. These infants were healthy before inoculation, and their detailed immunological profiles, including T cell and neutrophil levels, were within normal range. Most reported BCG cases involve impaired immunity, such as children with chronic granulomatous disease, severe combined immunodeficiency, or human immunodeficiency virus infections. Because of their immature immune systems, BCG vaccination can be hazardous even in early infants without immune abnormalities. Hence, we advise caution when administering BCG vaccines to early infants.

Key words BCG, disseminated BCG infection, infant, neutrophil, T cell.

Because the BCG Tokyo 172 strain used in the Japanese bacillus Calmette–Guerin (BCG) vaccine has extremely low pathogenicity among BCG substrains worldwide, the vaccine is generally considered safe.[1] There are several reports, however, of patients developing disseminated infection after receiving the Japanese BCG vaccine.[2] Although BCG infection has been reported in immunocompromised patients with chronic granulomatous disease (CGD), severe combined immunodeficiency (SCID), and interferon-γ (IFNγ) and interleukin-12 (IL-12) pathway defects,[2,3] as well as patients using immunosuppressive drugs or steroids, disseminated BCG infection is very rare but sometimes fatal. We report three cases of idiopathic disseminated BCG infection with lung lesions 22–34 days after vaccination in infants aged 3–4 months. Immunological analysis, including B-cell, T-cell, and neutrophil levels, were within normal ranges. To our knowledge, no previous reports of idiopathic disseminated BCG infection have included detailed evaluation of immune status. We report these cases and discuss the immature infant immune system.

Case reports

Case 1

A 4-month-old boy was admitted to hospital for fever and rash after BCG vaccination. He weighed 3780 g at birth after 40 weeks 6 days of gestation, and had no medical problems. He received BCG vaccination at 3 months 1 week of age and developed fever and redness at the inoculation site after 3 weeks. He also had redness around his eyes; we suspected differential diagnoses such as Kawasaki disease, a bacterial infection, or erythema polymorphism, and prescribed antibiotics. Because the rash extended to his whole body and the fever persisted, he was transferred to Kumamoto Regional Medical Center. He was 65 cm long, weighed 7200 g, had a body temperature of 38.7°C, and a heart rate of 160 beats/min. Erythema polymorphism was observed on his trunk and extremities (Fig. 1a). Superficial lymph nodes were not palpable. Laboratory findings included: white blood cell (WBC) count, 12 500/μL (neutrophils [Neut], 29%; lymphocytes [Ly], 60%; eosinophils [Eo], 6%; basophils [Baso], 0%; monocytes [Mo], 4%; atypical lymphocytes [Aty-Ly], 2%); red blood cell (RBC) count, 397×10^4/μL; hemoglobin (Hb), 10.4 g/dL; hematocrit (Hct), 30.9%; platelet count (Plt), 60.9×10^4/μL; C-reactive protein (CRP), 0.3 mg/dL. Blood biochemistry and urinalysis were normal. No significant bacteria such as acid-fast bacilli were detected in blood, gastric juice, or nasal cavity cultures. Real-time polymerase chain reaction (PCR) of gastric juice for *Mycobacterium tuberculosis* and tuberculin reaction and QuantiFERON TB-2G tests (QFT) were negative. Cerebrospinal fluid (CSF) cell counts did not change. Bone scintigraphy and chest radiography showed no abnormalities. Chest computed tomography (CT) showed multiple nodules in the right S4, S8, and basal segment as well as the left S8 (Fig. 1c); no enlarged lymphoid nodes were visible in the mediastinum. Abdominal echo and echocardiography showed no abscesses. Immunological tests showed normal immune body and complement levels. Flow cytometry lymphocyte blastoid formation test using phytohemagglutinin and lymphocyte surface marker analy-

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PLOS ONE

Kawasaki Disease-Specific Molecules in the Sera Are Linked to Microbe-Associated Molecular Patterns in the Biofilms

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Abstract

Background: Kawasaki disease (KD) is a systemic vasculitis of unknown etiology. The innate immune system is involved in its pathophysiology at the acute phase. We have recently established a novel murine model of KD coronary arteritis by oral administration of a synthetic microbe-associated molecular pattern (MAMP). On the hypothesis that specific MAMPs exist in KD sera, we have searched them to identify KD-specific molecules and to assess the pathogenesis.

Methods: We performed liquid chromatography-mass spectrometry (LC-MS) analysis of fractionated serum samples from 117 patients with KD and 106 controls. Microbiological and LC-MS evaluation of biofilm samples were also performed.

Results: KD samples elicited proinflammatory cytokine responses from human coronary artery endothelial cells (HCAECs). By LC-MS analysis of KD serum samples collected at 3 different periods, we detected a variety of KD-specific molecules in the lipophilic fractions that showed distinct m/z and MS/MS fragmentation patterns in each cluster. Serum KD-specific molecules showed m/z and MS/MS fragmentation patterns almost identical to those of MAMPs obtained from the biofilms formed *in vitro* (common MAMPs from *Bacillus cereus*, *Yersinia pseudotuberculosis* and *Staphylococcus aureus*) at the 1st study period, and from the biofilms formed *in vivo* (common MAMPs from *Bacillus cereus*, *Bacillus subtilis/Bacillus cereus/Yersinia pseudotuberculosis* and *Staphylococcus aureus*) at the 2nd and 3rd periods. The biofilm extracts from *Bacillus cereus*, *Bacillus subtilis*, *Yersinia pseudotuberculosis* and *Staphylococcus aureus* also induced proinflammatory cytokines by HCAECs. By the experiments with IgG affinity chromatography, some of these serum KD-specific molecules bound to IgG.

Conclusions: We herein conclude that serum KD-specific molecules were mostly derived from biofilms and possessed molecular structures common to MAMPs from *Bacillus cereus*, *Bacillus subtilis*, *Yersinia pseudotuberculosis and Staphylococcus aureus*. Discovery of these KD-specific molecules might offer novel insight into the diagnosis and management of KD as well as its pathogenesis.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

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Introduction

The etiology of Kawasaki disease (KD) remains unknown, however, KD has long been considered to be caused by an infectious agent, because of its characteristics of the symptoms, age distribution, seasonality, occurrence of community outbreaks and epidemic cycles. On the other hand, no consistently recoverable agents, lack of person-to-person transmission or a common

Category of manuscript: Original article

Title: Usefulness of two IFN-γ release assays for patients with rheumatic disease

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Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis under Treatment with Tocilizumab

Shumpei Yokota, Yasuhiko Itoh, Tomohiro Morio, Naokata Sumitomo, Kaori Daimaru and Seiji Minota

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EXTENDED REPORT

Tocilizumab in systemic juvenile idiopathic arthritis in a real-world clinical setting: results from 1 year of postmarketing surveillance follow-up of 417 patients in Japan

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ABSTRACT

Objectives To evaluate the safety and effectiveness of tocilizumab (TCZ) in patients with systemic juvenile idiopathic arthritis (sJIA) in real-world clinical settings in Japan.

Methods Paediatric patients with sJIA initiating TCZ between April 2008 and February 2012 and those previously enrolled in clinical trials who initiated TCZ before April 2008 were enrolled in a Japanese registry surveillance programme. Safety and effectiveness parameters were collected for 52 weeks.

Results Of 417 patients enrolled, mean age was 11.2 years and 48.0% were female. TCZ exposure was 407.0 patient-years (PYs). Baseline corticosteroid use was higher than in clinical trials. Rates of total adverse events (AEs) and serious AEs (SAEs) were 224.3/100 PYs and 54.5/100 PYs, respectively, with SAEs higher than previously reported. The most frequent AEs and SAEs were infections and infestations (69.8/100 PYs and 18.2/100 PYs, respectively). 74 serious infections occurred in 55 patients (18.2/100 PYs); higher than previously reported. 26 macrophage activation syndrome events were reported in 24 patients (6.4/100 PYs). Fever and rash symptoms improved from baseline to week 52 (54.6% to 5.6% and 43.0% to 5.6%, respectively). At 4 weeks, 8 weeks and 52 weeks, 90.5%, 96.2% and 99.0% of patients achieved normal C reactive protein levels (<0.3 mg/dL), respectively.

Conclusions These first real-world data demonstrated that TCZ was well tolerated, with acceptable safety and effectiveness in patients with sJIA. Higher incidences of SAEs and serious infections may be due to differences, such as corticosteroid use and concomitant diseases, between patient populations enrolled in previously reported clinical trials and this study.

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is a severe category of JIA characterised by prominent systemic features, such as fever, rash and serositis, and an onset before age 16 years. Patients are initially treated with non-steroidal anti-inflammatory drugs. As symptoms persist, corticosteroids are indicated.[1 2] However, an estimated half of all patients with JIA have been reported to have active disease after a 10-year period of observation, and long-term corticosteroid use has been associated with severe adverse effects, such as excessive weight gain, osteoporosis and growth suppression.[3 4] Moreover, treatment with methotrexate has not been shown to be effective in improving systemic features in patients with JIA.[5]

Interleukin 6 (IL-6) is a proinflammatory cytokine that is elevated in peripheral and synovial fluid and signals through the inflammatory biomarker C reactive protein (CRP). In patients with sJIA, IL-6 expression has been correlated with the extent and severity of joint involvement, with fever, and with platelet counts.[2 6] The humanised antihuman IL-6 receptor monoclonal antibody tocilizumab (TCZ) modulates IL-6 activity by blocking its binding to the soluble and membrane-bound IL-6 receptor and, consequently, lowers CRP levels. In clinical trials of patients with sJIA, including two phase II and two phase III trials, TCZ improved symptoms, such as fever and rash, and laboratory measurements, such as CRP, haemoglobin concentration and platelet counts, in patients with sJIA.[7–12] Adverse events (AEs) reported with TCZ treatment in patients with sJIA included infections, neutropenia and abnormalities in liver function test results. Most AEs were mild or moderate in severity and typical of those noted with other biologic agents, such as abatacept and canakinumab.[13 14] Notably, no or few cases, which resolved, of macrophage activation syndrome (MAS) were reported. On the basis of these results, TCZ was approved for the treatment of sJIA in Japan in 2008 and in the European Union and USA in 2011.

Clinical trials of TCZ in patients with sJIA had specific inclusion criteria and excluded patients with infections; concurrent medical or surgical conditions; leucopenia; thrombocytopenia; or concomitant diseases of the nervous, renal, endocrine or hepatic systems. Therefore, the data from these clinical trials may not fully represent the safety and effectiveness of TCZ for patients in real-world clinical settings. As a condition of approval of TCZ for the treatment of sJIA, the Japanese Health Authority required that an all-patient registry postmarketing surveillance (PMS) be conducted to investigate the safety and effectiveness of TCZ in real-world clinical settings in patients with sJIA. To our knowledge, this single-arm observational study is the first to evaluate the safety and effectiveness of TCZ in patients with sJIA in real-world clinical settings for as long as 52 weeks.

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ORIGINAL ARTICLE

Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial

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Abstract
Background To investigate the long-term outcome in children with frequently relapsing nephrotic syndrome (FRNS) we conducted a follow-up of a previous randomized controlled trial (RCT) 10 years after the initiation of the treatment protocol.
Methods We previously conducted an RCT on the efficacy of cyclosporine for treating children with FRNS. After 2 years of treatment, a recommended a management protocol of steroids, and immunosuppressants was provided.
Results Valid information was available for 46 of the 56 patients (82.1 %) enrolled in the original RCT. The median follow-up period was 10.3 years from the start of protocol treatment with cyclosporine. At last follow-up (mean age 18.7 years), only ten patients (21.7 %) showed disease-free remission (no relapse for at least 2 years). In contrast, 23 (50.0 %) continued to relapse frequently or were on immunosuppressants, eight patients (17.4 %) had infrequent relapses without immunosuppressants. Adverse effects attributable to treatment included short stature (6 patients), osteoporosis (six patients), obesity (4 patients), cataracts (3 patients) and hypertension (3 patients). No lethal event or renal dysfunction occurred during follow-up.
Conclusions This 10-year follow-up study shows that most children with FRNS experience relapses after 2 years of cyclosporine treatment, in adolescence and into adulthood. Outcomes in terms of life expectancy and renal function are favorable.

Keywords Children · Follow-up · Long-term · Nephrotic syndrome · Randomized · Controlled trial · Non-remission

The results were presented in abstract form at the 43nd Annual American Society of Nephrology Conference.

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CONCISE COMMUNICATION

Familial Mediterranean fever variant with repeated atypical skin eruptions

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ABSTRACT

Familial Mediterranean fever (FMF) is characterized by self-limited bouts of fever and polyserositis. Skin involvement is not common in FMF, and erysipelas-like erythema is found to be the most frequent skin eruption which is often accompanied by arthritis and fever, and disappears within 12–72 h. We report a 40-year-old Japanese woman who presented with a 2-year history of recurrent fever with general fatigue, polyarthralgia and transient maculopapular eruptions on her lower extremities and trunk. The histological findings of the maculopapular eruption showed lymphocyte infiltration around the capillaries in the entire dermis. Mutation analysis showed a heterozygous E148Q-P369S mutation of *MEFV*. These findings suggested a diagnosis of late-onset FMF variant with atypical skin eruptions. The patient was successfully treated with colchicine. Thus, we should pay attention to repeated atypical skin eruptions for the early detection of atypical FMF.

Key words: autoinflammatory disease, colchicine, erysipelas-like erythema, familial Mediterranean fever, *MEFV*.

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessively inherited autoinflammatory disease characterized by self-limited bouts of fever and polyserositis.[1] In addition to recurrent febrile attacks, sterile peritonitis, pleuritis and arthritis are frequently seen in FMF. Onset usually occurs in childhood, and reactive amyloidosis may be a life-threatening complication in adult life. Skin involvement is not common, with a frequency of 12% in 470 children with FMF, as indicated in a previous study.[2] If reported, erysipelas-like erythema is found to be the most common skin eruption in FMF. The typical lesions are warm, tender, erythematous plaques with well-defined borders usually located on the lower extremities around the dorsum of the foot or malleolus. Although the lesions are often accompanied by arthralgia and fever,[3] they disappear within 12–72 h.[4]

We here report the case of a patient with late-onset FMF variant and atypical skin eruptions, who was successfully treated with colchicine.

CASE REPORT

A 40-year-old Japanese woman presented with a 2-year history of recurrent fever with general fatigue and polyarthralgia. Two years before, she had been treated with 20 mg/day hydrocortisone for hypothalamic hypoadrenalism, and antibiotics for 4 weeks for infectious endocarditis, but both these therapies were ineffective. At 40 years of age, she noticed transient maculopapular eruptions which were 2–5 mm in diameter (Fig. 1a) without itch on her lower extremities and trunk with a high-grade fever (>40°C) that persisted for 12–72 h, arthralgia, abdominal pain and diarrhea. These eruptions disappeared simultaneously with other symptoms. The histological findings of the maculopapular eruptions showed lymphocyte infiltration around the capillaries in the entire dermis (Fig. 1b,c). The patient had undergone pancreatoduodenectomy since severe acute pancreatitis was diagnosed on the basis of the abdominal pain, vomiting, diarrhea and elevated serum amylase level (571 IU/L; normal, 33–120). Acute pancreatitis was histopathologically proven. However, the periodic fever, general fatigue, polyarthralgia and transient maculopapular eruptions with erythema on her lower extremities and abdomen recurred (Fig. 1c). Skin eruptions were basically similar to those on the first consultation, and some eruptions appeared clustering and some discretely. Most laboratory data including ferritin, adrenocorticotropic hormone, cortisol and interleukin-18 (169.6 pg/mL; normal, <200) levels were within the normal ranges, except that leukocyte count was 9260/μL (normal, 3300–7900; neutrophils, 75.5%), hemoglobin concentration 9.1 g/dL (normal, 11.3–15.4), C-reactive protein 7.91 mg/dL (normal, <0.2) and the antinuclear antibody titer was 160 (speckled pattern; normal, <40). We considered FMF as a diagnosis, and adult-onset Still's disease (AOSD) as a differential diagnosis. AOSD was denied because of fever and arthralgia

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LETTER TO THE EDITOR

Familial Mediterranean fever with onset in the 70s showing various neutrophilic dermatosis

Editor

A 73-year-old Japanese man diagnosed with Sweet's syndrome was referred to our hospital because of the refractory high fever and vaguely circumscribed indurated erythemas on his lower extremities in 2009 (Fig. 1). Blood examination showed elevated levels of white blood cell count (11,800/mm^3) and C-reactive protein (15.03 mg/dl). Although his parents were married between close relatives, there was no one with similar symptoms in his family. Histopathological examination from a skin biopsy revealed perivascular and interstitial inflammatory cells infiltration (Fig. 2a). Within a few days, his symptoms dramatically improved. When his symptoms recurred, repeated skin biopsy showed significant oedema in the superficial dermis and dense diffuse inflammatory cell infiltration (Fig. 2b). Systemic work-up showed no evidences of malignancy. Diagnostic criteria of any collagen diseases were not met. Repeated blood cultures were negative. Afterwards, episodic high fever with occasional arthralgia and myalgia on his extremities repeatedly appeared every 2–4 weeks, which usually improved spontaneously within 2 days to a week. Paroxysmal polyserositis was not observed. Another skin biopsy showed focal vasculitis in the dermis and subcutis with neutrophilic infiltration (Fig. 2c).

According to the Tel Hashomer criteria,[1] we diagnosed our case with Familial Mediterranean fever (FMF). Mutation analysis of Mediterranean fever (MEFV) gene and tumour necrosis factor receptor superfamily 1A gene were performed as described previously.[2,3] It revealed heterozygous L110P/E148Q/G304R alterations in exon 2. Serum cytokine levels were measured using MILLIPLEX MAP Human Cytokine Panel (MERCK MILLIPORE, Tokyo, Japan) shown in Table 1. IL-1β, IL-6 and TNF-α were all higher during the attack than between the attacks. Regarding the treatment, colchicine at 2 mg a day seemed to be efficacious; however, severe diarrhoea developed as an adverse effect. No drugs could prevent the febrile attacks. To date, his symptoms still remain recurrent.

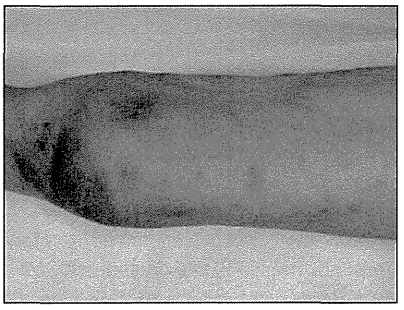

Figure 1 Vaguely circumscribed tender indurated erythemas were observed.

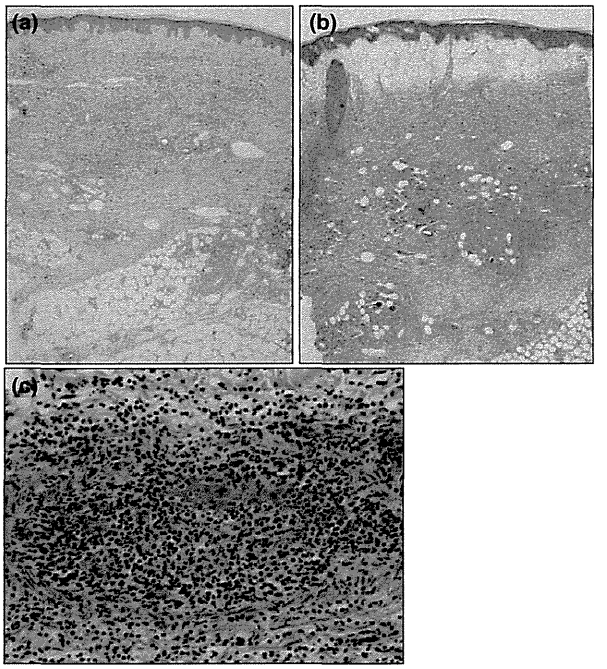

Figure 2 (a) Histopathological findings of the indurated erythema. Perivascular and interstitial infiltration of lymphocytes, histiocytes and few polynuclear cells are demonstrated in the dermis and subcutis. Leukocytoclastic vasculitis was not demonstrated [haematoxylin–eosin (H-E) staining, original magnification ×40]. (b) Findings of repeated histological examination. Significant oedema in the superficial dermis and dense diffuse inflammatory cell infiltration mainly composed of neutrophils and lymphocytes in the dermis and subcutis are observed. Leukocytoclastic vasculitis was not demonstrated (H-E staining, original magnification ×40). (c) Findings of another histological examination. In the subcutis, perivascular inflammatory cell infiltration with nuclear dust, extravasation of red blood cells and fibrinoid degeneration of the wall of the blood vessels are observed (H-E staining, original magnification ×200).

RHEUMATOLOGY

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Concise report

Dysregulated mature IL-1β production in familial Mediterranean fever

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Abstract

Objective. The aim of this study was to analyse the role of circulating cleaved IL-1β in patients with FMF.

Methods. We enrolled 20 patients with FMF (5 males and 15 females), 22 patients with RA (4 males and 18 females) and 22 healthy controls (6 males and 16 females). Serum levels of serum amyloid A (SAA) were measured by ELISA. We also determined whether IL-1β was present as the cleaved form (p17) in the sera of FMF patients by immunoblotting using anti-cleaved IL-1β antibody.

Results. Although SAA concentrations were elevated in the sera, there was no significant difference in these concentrations between FMF patients and RA patients. Immunoblot analysis demonstrated that the cleaved form of IL-1β (p17) was present in sera from FMF patients during febrile attack periods, but not in healthy controls. Bands representing the cleaved form of IL-1β were not detected in serum from FMF patients at non-febrile attack periods or remission periods under colchicine treatment. The amounts of cleaved IL-1β (p17) were significantly higher in patients with FMF compared with those in patients with RA in the inflammatory phase.

Conclusion. The cleaved form of IL-1β is a valuable biomarker for monitoring disease activity and response to colchicine treatment in patients with FMF. It might be useful to discriminate FMF from other non-IL-1β-mediated inflammatory disorders.

Key words: IL-1β, familial Mediterranean fever, biomarker, autoinflammatory disease, serum amyloid A.

CLINICAL SCIENCE

Introduction

FMF is the most common human hereditary autoinflammatory disorder, characterized by recurrent, self-limited bouts of fever and localized inflammation, usually involving the peritoneum, pleura and joints [1]. These episodes of inflammation are caused mainly by a massive influx of neutrophils into serous cavities and are accompanied by elevation of acute phase reactants [2]. The effectiveness of anti-IL-1β treatment has suggested that IL-1β plays a role in the pathophysiology of the disease [3]. However, dysregulated IL-1β induction in patients with FMF has been demonstrated in few studies [4].

FMF is caused by mutations within the Mediterranean fever (*MEFV*) gene, which encodes pyrin, a protein that has been proposed to exert a suppressive effect on inflammasome activation [5]. This inhibitory control mechanism is lost through mutations within the *MEFV* gene [6]. This hypothesis is supported by *ex vivo* evidence where mononuclear cells isolated from patients with FMF showed enhanced IL-1β production [4]. However, actual serum levels of IL-1β have not been reported, indicating a disparity with the *in vitro* findings. Furthermore, the role of IL-1β in the pathogenesis of FMF and its measurement

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SHORT COMMUNICATION

Serum IL-18 as a potential specific marker for differentiating systemic juvenile idiopathic arthritis from incomplete Kawasaki disease

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Abstract Clinical features and laboratory parameters in patients with incomplete Kawasaki disease (KD) and systemic juvenile idiopathic arthritis (s-JIA) tend to overlap. Furthermore, there have been no definite biomarkers for these diseases. This situation makes the clinical diagnosis of these patients difficult. In this study, we aimed to measure serum interleukin (IL)-18 and IL-6 levels in patients with s-JIA who were initially diagnosed with incomplete KD and compare these data with those in patients with complete KD and arthritis. Serum IL-18 levels in patients with s-JIA were significantly elevated compared with those in patients with KD and arthritis. Pediatricians should be aware that the presentation of s-JIA can mimic incomplete KD. Because the clinical features overlap, a high index of suspicion is warranted. The measurement of serum IL-18 may be useful for differentiating s-JIA from KD.

Keywords Interleukin 18 · Systemic juvenile idiopathic arthritis · Incomplete Kawasaki disease

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Introduction

Kawasaki disease (KD) is one of the most common childhood vasculitis disorders. However, there are some patients who do not fulfill the classic diagnostic criteria for KD and are termed as incomplete KD. It is important to recognize and treat this entity because it is not a milder form of KD, and it carries a risk of coronary artery aberrations similar to that of complete KD [1]. For this reason, physicians possibly diagnose patients with KD prematurely, even though they do not meet the complete diagnostic criteria, in the fear of losing the opportunity to administer high-dose intravenous immunoglobulin (IVIG) and for preventing the potentially life-threatening complication of coronary aneurysm.

Furthermore, it has been reported that some patients with KD have arthritis [2]. Systemic juvenile idiopathic arthritis (s-JIA) is characterized by remitting fever, a typical skin rash, and arthritis. Diagnosis of s-JIA is often challenging, particularly before children have had symptoms for 6 weeks as required by the International League of Associations for Rheumatology and American College of Rheumatology criteria [3]. Pericardial effusion is a well-recognized feature of s-JIA along with myocarditis, which is a rare feature [4]. Coronary artery dilation has been recently identified as one of the cardiac manifestations in patients with s-JIA [5].

Differentiation of KD and s-JIA is important to avoid multiple courses of IVIG because of suspected refractory KD; however, clinical features and laboratory parameters in patients with s-JIA and incomplete KD tend to overlap. Furthermore, there are no definite biomarkers for these diseases, which makes the clinical diagnosis of these patients difficult [6–9].

We recently reported that serum levels of IL-18 are highly elevated in patients with s-JIA, and the abnormal

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Interleukin-18 for predicting the development of macrophage activation syndrome in systemic juvenile idiopathic arthritis

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ABSTRACT

To assess the role of IL-6/IL-18 in the pathogenesis of systemic juvenile idiopathic arthritis (s-JIA) and to investigate the clinical significance of serum IL-18 levels for predicting macrophage activation syndrome (MAS) development, we measured the serum IL-6/IL-18 levels in 76 s-JIA patients, including 15 with MAS, and compared them with the clinical features. We identified 2 distinct subsets on the basis of serum IL-6/IL-18 levels. The IL-18-dominant subset had more patients who developed MAS. Serum IL-18 levels during active phase in patients with MAS were significantly higher than those without MAS. The cutoff value of serum IL-18 levels for predicting MAS development was 47750 pg/ml. The patients with IL-18 dominant subset at their disease onset were significantly more likely to develop MAS after TCZ therapy started. IL-18 might have a key role in the pathogenesis of MAS. Serum IL-18 levels >47750 pg/ml might be useful to predict MAS development.

1. Introduction

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of systemic juvenile idiopathic arthritis (s-JIA) [1]. MAS occurs in approximately 7%–13% patients with s-JIA [2]. Some evidence suggests a prevalence of subclinical MAS in another 30%–40% patients [3,4]. A variety of triggers have been implicated in the pathogenesis of MAS associated with s-JIA, including viral infections and therapy with nonsteroidal anti-inflammatory drugs, methotrexate, and etanercept [5–7]. The hallmark of MAS is an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T lymphocytes and macrophages, which leads to marked hypercytokinemia [8]. It is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, profound depression of all 3 blood-cell lines, deranged liver function, intravascular coagulation, and central nervous system dysfunction [9]. A characteristic feature is seen on bone marrow examination, which reveals, though not always, numerous morphologically benign macrophages exhibiting hemophagocytic activity. MAS should be considered among the secondary causes of hemophagocytic lymphohistiocytosis (HLH) because of a close resemblance to a group of HLH syndromes [10,11].

MAS is a potentially fatal disease; therefore, a timely and prompt diagnosis is essential to initiate life-saving treatment. However, it can be difficult to distinguish MAS from conditions that may mimic some of its features, such as s-JIA flares or sepsis-like syndromes. Differentiation of MAS from these conditions is essential to select the appropriate therapeutic interventions in a timely fashion. However, there is no definite clinical or laboratory parameter that establishes MAS diagnosis.

Recent investigations into the pathophysiology of s-JIA have focused on mediators of the innate immune system. In particular, serum interleukin (IL)-1, IL-6, and IL-18 levels are correlated with disease activity and secondary complications [12–14]. We previously reported serum IL-18 levels are increased in active s-JIA. Thus, serum IL-18 levels are increasingly used as a biomarker for s-JIA diagnosis and of its therapeutic response in s-JIA [15]. Serum IL-18 levels are even further increased in patients with s-JIA-related MAS, and this increase seems to be specific because other forms of secondary HLH are associated with lower serum IL-18 levels [15–17]. Furthermore, our preliminary data showed that there are 2 subsets of patients with s-JIA having certain distinct clinical features on the basis of IL-6 and IL-18 levels [18]. Patients in the IL-6-dominant subset (IL-18/IL-6 < 1000) appeared to have more severe joint disease, whereas those in the IL-18-dominant subset (IL-18/IL-6 > 1000) were more likely to develop MAS [18].

To assess the role of IL-6 and IL-18 in the pathogenesis of s-JIA and, in particular, to investigate the clinical significance of the serum IL-6 and IL-

Abbreviations: s-JIA, systemic juvenile idiopathic arthritis; MAS, macrophage activation syndrome; IL, interleukin; HLH, hemophagocytic lymphohistiocytosis; TCZ, tocilizumab; PSL, predonisolone; CRP, C-reactive protein; AOSD, adult onset Still's disease.

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BRIEF COMMUNICATION

Severe and Rapid Progression in Very Early-Onset Chronic Granulomatous Disease-Associated Colitis

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Abstract
Purpose Chronic granulomatous disease (CGD) is a primary immunodeficiency disease that leads to recurrent infection and hyper-inflammation, occasionally represented by CGD-associated colitis (CGD colitis). Although clinical symptoms of CGD colitis mimic those of ulcerative colitis (UC), there is no reliable standard measurement of disease activity or standard therapeutic strategy for CGD colitis. Here, we examined the clinical manifestation of CGD colitis based on severity using a noninvasive measure of disease activity, the Pediatric Ulcerative Colitis Activity Index (PUCAI), which has been validated and widely used for pediatric UC.
Methods Sixteen of 35 CGD patients, who were diagnosed with CGD colitis based on colonoscopic and histological findings, were examined using the PUCAI. Both the PUCAI and the physician global assessment (PGA) tool were retrospectively scored by reviewing medical records.
Results Disease activity defined by PUCAI was correlated with PGA, and increased at diagnosis of CGD colitis, especially in patients who were younger than 6 years of age (very early-onset CGD colitis: VEO-CGD colitis) when diagnosed with CGD colitis. All severe patients had a more progressive form of VEO-CGD colitis. Unlike mild and moderate patients, severe patients required multidrug therapy of corticosteroids and immunomodulator/immunosuppressants, and some were eventually treated with hematopoietic stem cell transplantation.
Conclusions Although the validation of PUCAI in CGD colitis should be considered for future use, our results indicate that noninvasive measures could be effective to measure disease activity and help to determine suitable treatment for CGD colitis. In patients with VEO-CGD colitis, multidrug therapy would need to be considered at an early stage on the basis of disease activity.

Keywords Chronic granulomatous disease · CGD colitis · inflammation · granuloma · pediatric ulcerative colitis activity index · very early-onset CGD colitis

Highlights • Disease activity defined by PUCAI increased at diagnosis of CGD colitis
• Patients with very early-onset CGD colitis had an aggravated and more progressive form of the condition
• Severe patients with very early-onset CGD colitis required multidrug therapy

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Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency disease characterized by the failure of the nicotinamide adenine dinucleotide phosphate (NADPH) enzyme system in phagocytes to produce reactive oxygen species. The frequency of severe infection has been reported as 0.26–0.3 times per year in CGD patients [1, 2]. Hyperinflammation, represented by gastrointestinal involvement, including obstructive gastrointestinal granuloma, perirectal abscess or fistula, and CGD-associated colitis (CGD colitis), develops in 18

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CORRESPONDENCE

Tocilizumab is effective in a familial Mediterranean fever patient complicated with histologically proven recurrent fasciitis and myositis

Dear Editor,

Familial Mediterranean fever (FMF) is an autoinflammatory disease. Its major clinical manifestations are recurrent paroxysmal fever, serositis and arthritis. Activated neutrophils are involved in the pathogenesis of FMF and abundant neutrophils are found in the affected regions of individuals with FMF.[1] Although myalgia is well documented in FMF patients, the

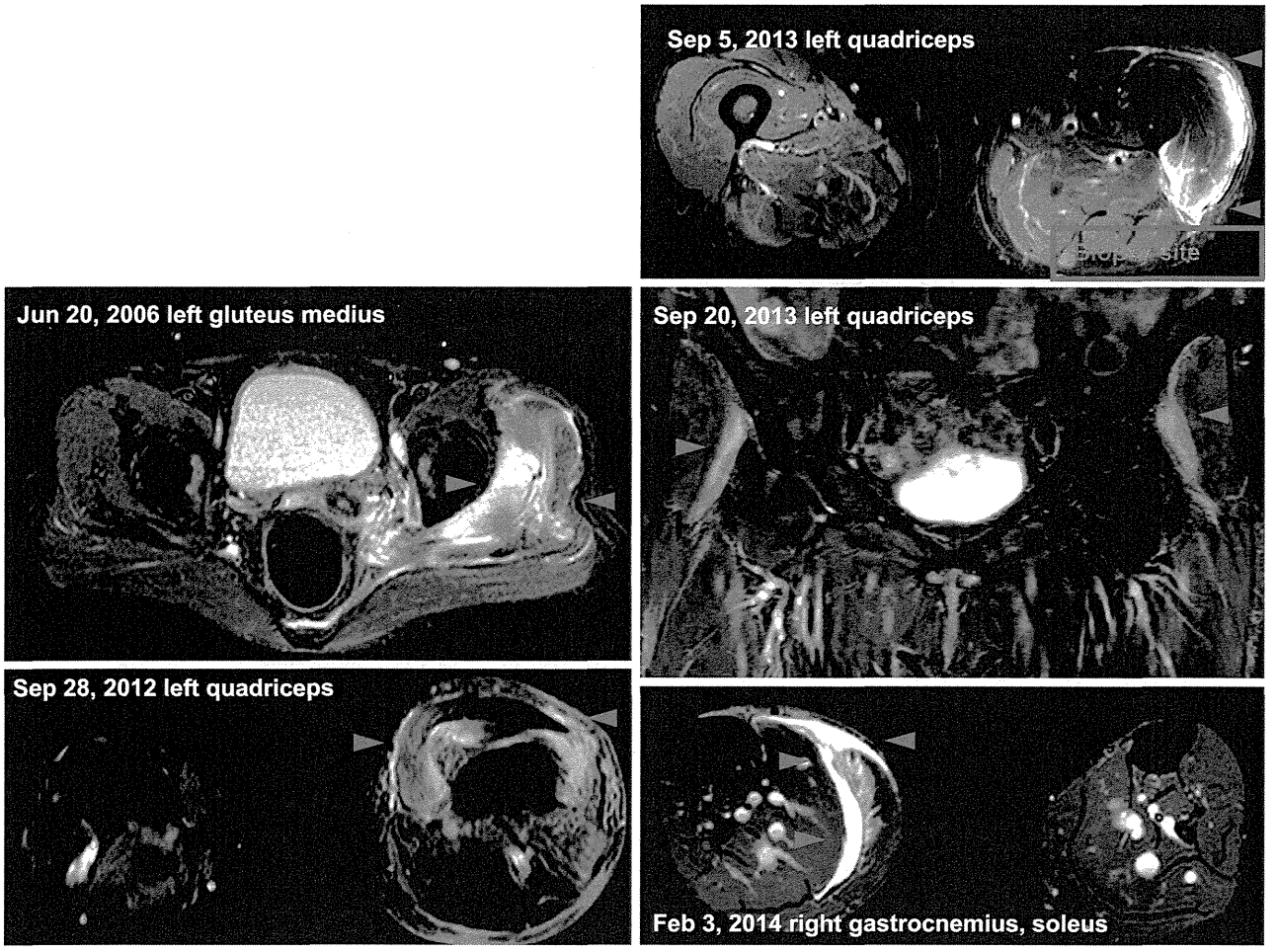

Figure 1 Magnetic resonance imaging (short TI inversion recovery) of the lower limbs of the patient. High intensity of fascia and muscle appeared in different sites in each attack.

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CONCISE COMMUNICATION

Psoriasis-like lesions in a patient with familial Mediterranean fever

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ABSTRACT

Familial Mediterranean fever (FMF) is a rare hereditary autoinflammatory disorder that is caused by pyrin gene mutation associated with aberrance of the interleukin (IL)-1β pathway and characterized by recurrent, self-limiting attacks of fever and other inflammatory symptoms. We report a case of FMF with annular erythema and psoriasis-like lesions, the latter of which demonstrated parakeratosis with neutrophil microabscesses and mild inflammatory mononuclear cell infiltration in the upper dermis. Immunofluorescence staining showed IL-17-positive T-cells. Skin eruption with neutrophil migration in the epidermis may be provoked by T-helper 17 cell activation through the abnormal IL-1β cascade in FMF.

Key words: **familial Mediterranean fever, interleukin-1β, interleukin-17, neutrophil, psoriasis-like lesions.**

INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disorder caused by the abnormal function of pyrin, which is encoded by the Mediterranean fever (*MEFV*) gene.[1] It is clinically characterized by self-resolving bouts of fever accompanied by peritonitis, pleuritis and arthritis. The most characteristic cutaneous manifestation is erysipelas-like erythema often located on the lower legs, the frequency of which ranges 3–46%.[1] Fewer cases exhibit Henoch–Schönlein purpura,[1] scattered purpuric lesions,[1] bullous lesions,[2] panniculitis[3] and polyarthritis nodosa.[4]

In the present case, the clinical appearance and histopathology of the skin lesions resembled psoriasis. Recently, a case of juvenile psoriatic arthritis with sacroiliitis in a Turkish girl carrying *MEFV* gene mutations was reported.[5] We predicted that FMF and psoriatic change may be related to pathogenic mechanisms involving the cytokine profile.

CASE REPORT

A 45-year-old woman was referred to us for evaluation of a rash, arthralgia, back pain and generalized muscular pain with a 4-day history of a high fever. She had non-indurated erythema on her face, neck, trunk and extremities without pain (Fig. 1a). Similar skin lesions had developed 2–4-times/year over the previous 3 years, accompanied by periodic febrile episodes. She had also experienced painful red swelling of her left forearm 1 month previously. She had suffered from a fatty liver and hyperlipidemia for more than 2 years without treatment. Her family history was unremarkable. Laboratory investigations, including white blood cell count and C-reactive protein, were within normal limits, but transaminase and triglyceride levels were moderately elevated. Rheumatoid factor and antinuclear antibody were negative. The symptoms, including cutaneous manifestations, completely disappeared within 1 week. Subsequently, small red macules appeared on her trunk, upper arms and thighs which were generally less than 5 mm in diameter and covered with fine scales (Fig. 1b). Histopathological examination of the small macules resembled psoriasis.

Owing to her history of periodic fever and other symptoms, genetic analysis of FMF was performed. She had homozygous p.E148Q and heterozygous p.L110P mutations in the *MEFV* gene. The febrile attack of higher than 40°C disappeared following administration of a daily dose of colchicine up to 1.0 mg, while low-grade fever of 37–38°C with muscular pain persisted and new small macular lesions developed continuously. Moreover, she was unable to tolerate increased doses of colchicine owing to severe gastrointestinal upset. Therefore, maxacalcitol ointment was topically applied to the cutaneous lesions, which resulted in moderate improvement.

Six months later, she came to us because of a 3-week history of multiple macular erythema with strong pruritus confined to sun-exposed areas. They were confined to the face,

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Increased prevalence of *MEFV* exon 10 variants in Japanese patients with adult-onset Still's disease

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Summary

Autoinflammatory diseases include a large spectrum of monogenic diseases, e.g. familial Mediterranean fever (FMF), as well as complex genetic trait diseases, e.g. adult-onset Still's disease (AOSD). In populations where FMF is common, an increased *MEFV* mutation rate is found in patients with rheumatic diseases. The aim of this study was to examine *MEFV* mutations in Japanese patients with AOSD. Genomic DNA was isolated from 49 AOSD patients and 105 healthy controls, and exons 1, 2, 3 and 10 of the *MEFV* gene genotyped by direct sequencing. *MEFV* mutation frequencies in AOSD patients were compared with controls. We found no significant difference in overall allele frequencies of *MEFV* variants between AOSD patients and controls. However, *MEFV* exon 10 variants (M694I and G632S) were significantly higher in AOSD patients than controls (6·1 *versus* 0%). In addition, there was no significant difference between *MEFV* variant carriers and non-carriers with clinical manifestations, but the monocyclic clinical course of the AOSD disease phenotype was observed less frequently in patients without *MEFV* variants. AOSD patients had significantly higher frequencies of *MEFV* exon 10 mutations, suggesting that low-frequency variants of *MEFV* gene may be one of the susceptibility factors of AOSD.

Keywords: adult-onset Still's disease, autoinflammatory disease, *MEFV*

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease characterized by fever, skin rash, and joint pain [1]. The pathophysiology of AOSD has remained unclear; however, it is presumed to be an autoinflammatory disease due to the absence of autoantibodies and autoantigen-specific T cells [2]. Patients with autoinflammatory diseases, including classical hereditary periodic syndromes, share clinical features (e.g. spiking fever, skin rash, and arthritis) with the major symptoms of AOSD [3]. Familial Mediterranean fever (FMF) is a common autoinflammatory disease, characterized by recurrent inflammatory attacks of fever, skin rash, synovitis, and serositis [4]. FMF is thought to be caused by gain-of-function mutations in the *MEFV* gene [5]. Although AOSD etiology and pathogenesis are largely unknown, a growing number of studies support the hypothesis that similar to other autoinflammatory diseases, dysregulation of inflammasome activation and the related overproduction of interleukin-1 (IL-1) β plays a pivotal role [6]. Accordingly, IL-1 blockade shows efficacy in treating AOSD symptoms in refractory cases [7]. Recent advances in sequencing technology are allowing investigators to sequence selected genes to discover low-frequency variants in patients with complex and genetically matched controls [8]. Thus, we propose that *MEFV* mutations/polymorphisms may be one of the genetic factors associated with AOSD. Therefore, in this study we investigated *MEFV* gene variations in Japanese AOSD patients.

