why KS is characterized by systemic vasculitis (Maeno *et al*, 1998; Ohno *et al*, 2000).

Serum and platelet VEGF levels before IVIG were higher in the non-responder group than those in the responder group, but this difference was not statistically significant. With regard to serum VEGF levels, a similar result was shown in a previous report (Terai *et al*, 2003). However, compared to the changes in serum and platelet VEGF levels before and after IVIG treatment, only platelet VEGF levels were decreased after IVIG in the responder group, which reflects the reactivity of the treatment. Large amounts of vascular growth factors, such as VEGF and platelet-derived growth factor are released from activated platelets at the site of injured endothelial cells (Möhle *et al*, 1997). Sustained levels of platelet VEGF after IVIG may reflect severe endothelial injury promoting the vicious cycle of cardiovascular complications by activating matrix metalloproteinases (MMPs). Based on our findings, platelet VEGF levels may reflect the reactivity of IVIG treatment in KS patients.

Low platelets counts are one of the IVIG unresponsiveness markers that indicate an increased risk for CAA (Kobayashi *et al*, 2006). Our study showed that lower platelet counts of before IVIG treatment were associated with higher levels of platelet VEGF in KS patients, while there was no correlation in controls. In KS, enhanced platelet aggregation was noted at a high frequency before IVIG treatment (Taki *et al*, 2003). Platelet aggregation induced thrombocytopenia, leading to enhanced marrow stromal cell production of thrombopoietin and increased thrombopoiesis (Kaushansky, 2005; Kirito & Kaushansky, 2005). Thus, newly produced megakaryocytes and platelets contain more abundant amounts of platelet VEGF in their cytoplasm than mature platelets, and activated platelets aggregate and release platelet VEGF at the endothelial injury vascular sites. Our data also supports the idea that KS is involved in vascular inflammation accompanied by platelet reactivity and is distinct from bacterial infectious disease. Platelet VEGF levels are likely to be related to pathological development associated with systemic vasculitis, such as in KS.

In this study, platelet VEGF levels before IVIG treatment correlated with the CAA *z*-score while serum VEGF levels did not. VEGF induces MMPs, which degrade extracellular matrix components (Sato, 1998). Histopathology has also shown abundant expression of VEGF, flt-1, and MMPs at the site of coronary lesions in KS patients (Suzuki *et al*, 2000; Yasukawa *et al*, 2002; Gavin *et al*, 2003). By inducing MMPs, VEGF accelerates the infiltration of inflammatory cells and is implicated in the degradation of the extracellular matrix. Therefore, it seems likely that increased levels of platelet VEGF would promote CAA development. However, it is unclear why platelet VEGF levels were significantly correlated with the CAA *z*-score, while no significant differences of platelet VEGF levels were seen between the IVIG responder group and IVIG non-responder group before IVIG treatment. IVIG unresponsiveness may be influenced not only by the severity of vasculitis, but also by multiple factors, such as genetic background or immunological abnormalities (Onouchi *et al*, 2008).

Interestingly, our study showed that platelet VEGF levels were strongly correlated with MPV. MPV is associated with platelet reactivity and high MPV levels are also correlated with diabetes mellitus, hypertension and myocardial infarction with coronary heart disease (Endler *et al*, 2002; Nadar *et al*, 2004; Papanas *et al*, 2004; Khandekar *et al*, 2006). Newly released platelets with higher α granule content are larger and more reactive than mature platelets (Karpatkin, 1969; Karpatkin & Strick, 1972). The increase in MPV suggests consumption of platelets and compensatory production from bone marrow. These data indicate that the changes of MPV levels might be useful for evaluating the reactivity of IVIG treatment, and a high rate of platelet turnover may be associated with platelet reactivity and developing CAA in KS.

The present study showed that platelet VEGF levels were useful for evaluating the severity of KS. A close relationship between platelet VEGF and MPV levels suggest that MPV could be substituted for platelet VEGF, and might be a reliable marker for evaluating the severity of vasculitis, which could be applied in the treatment of KS. Further studies are necessary to examine the usefulness of this application.

In conclusion, platelet VEGF levels reflect platelets' biological properties and the severity of vasculitis, and they are a useful predictor for prognosis in KS.

Acknowledgements

This study is supported by the Ministry of Health, Labour and Welfare (MHLW), Health and Labour Sciences Research Grants, Comprehensive Research on Practical Application of Medical Technology: a Randomized Controlled Trial to Assess Immunoglobulin Plus Steroid Efficacy for Kawasaki Disease (RAISE) Study.

References

Arisato, T., Hashiguchi, T., Sarker, K.P., Arimura, K., Asano, M., Matsuo, K., Osame, M. & Maruyama, I. (2003) Highly accumulated platelet vascular endothelial growth factor in coagulant thrombotic region. *Journal of Thrombosis Haemostasis*, **1**, 2589–2593.

Ayusawa, M., Sonobe, T., Uemura, S., Ogawa, S., Nakamura, Y., Kiyosawa, N., Ishii, M. & Harada, K. , Kawasaki Disease Research Committee (2005) Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatrics International*, **47**, 232–234.

Cesari, F., Marcucci, R., Caporale, R., Paniccia, R., Romano, E., Gensini, G.F., Abbatem, R. & Gori, A.M. (2008) Relationship between high platelet turnover and platelet function in high-risk patients with coronary artery disease on dual antiplatelet therapy. *Thrombosis and Haemostasis*, **99**, 930–935.

Endler, G., Klimesch, A., Sunder-Plassmann, H., Schillinger, M., Exner, M., Mannhalter, C., Jordanova, N., Christ, G., Thalhammer, R., Huber, K. & Sunder-Plassmann, R. (2002) Mean platelet volume is an independent risk factor for myocardial infarction but not for

coronary artery disease. *British Journal of Haematology*, **117**, 399–404.

Ferrara, N., Gerber, H.-P. & LeCouter, J. (2003) The biology of VEGF and its receptors. *Nature Medicine*, **9**, 669–676.

Furukawa, S., Matsubara, T., Yone, K., Hirano, Y., Okumura, K. & Yabuta, K. (1992) Kawasaki disease differs from anaphylactoid purpura and measles with regard to tumour necrosis factor-alpha and interleukin 6 in serum. *European Journal of Pediatrics*, **151**, 44–47.

Gavin, P.J., Crawford, S.E., Shulman, S.T., Garcia, F.L. & Rowley, A.H. (2003) Systemic arterial expression of matrix metalloproteinases 2 and 9 in acute Kawasaki disease. *Arteriosclerosis Thrombosis and Vascular Biology*, **23**, 576–581.

Giles, H., Smith, R.E. & Martin, J.F. (1994) Platelet glycoprotein IIb-IIIa and size are increased in acute myocardial infarction. *European Journal of Clinical Investigation*, **24**, 69–72.

Hashiguchi, T., Arimura, K., Matsumuro, K., Otsuka, R., Watanabe, O., Jonosono, M., Maruyama, Y., Maruyama, I. & Osame, M. (2000) Highly concentrated vascular endothelial growth factor in platelets in Crow-Fukase syndrome. *Muscle and Nerve*, **23**, 1051–1056.

Jakubowski, J.A., Thompson, C.B., Vaillancourt, R., Valeri, C.R. & Deykin, D. (1983) Arachidonic acid metabolism by platelets of differing size. *British Journal of Haematology*, **53**, 503–511.

Jerelyn, W. & Patricia, G. (2000) Performance Evaluation of the Sysmex XE-2100 Hematology Analyzer. *Laboratory Hematology*, **6**, 83–92.

Karpatkin, S. (1969) Heterogeneity of human platelets. I. Metabolic and kinetic evidence suggestive of young and old platelets. *Journal of Clinical Investigation*, **48**, 1073–1082.

Karpatkin, S. & Strick, N. (1972) Heterogeneity of human platelets. V. Differences in glycolytic and related enzymes with possible relation to platelet age. *Journal of Clinical Investigation*, **51**, 1235–1243.

Kato, H., Koike, S., Yamamoto, M., Ito, Y. & Yano, E. (1975) Coronary aneurysms in infants and young children with acute febrile mucocutaneus lymph node syndrome. *Journal of Pediatrics*, **86**, 892–898.

Kaushansky, K. (2005) The molecular mechanisms that control thrombopoiesis. *Journal of Clinical Investigation*, **115**, 3339–3347.

Kawasaki, T., Kosaki, F., Okawa, S., Shigematsu, I. & Yanagawa, H. (1974) A new infantile acute febrile mucocutaneus lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics*, **54**, 271–276.

Khandekar, M.M., Khurana, A.S., Deshmukh, S.D., Kakrani, A.L., Katdare, A.D. & Inamdar, A.K. (2006) Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: an Indian scenario. *Journal of Clinical Pathology*, **59**, 146–149.

Kimura, K., Hashiguchi, T., Deguchi, T., Horinouchi, S., Uto, T., Oku, H., Setoyama, S., Maruyama, I., Osame, M. & Arimura, K. (2007) Serum VEGF – as a prognostic factor of atherosclerosis. *Atherosclerosis*, **194**, 182–188.

Kirito, K. & Kaushansky, K. (2005) Thrombopoietin stimulates vascular endothelial cell growth factor (VEGF) production in hematopoietic stem cells. *Cell Cycle*, **4**, 1729–1731.

Kobayashi, T., Inoue, Y., Takeuchi, K., Okada, Y., Tamura, K., Tomomasa, T., Kobayashi, T. & Morikawa, A. (2006) Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*, **113**, 2606–2612.

Kurotobi, S., Nagai, T., Kawakami, N. & Sano, T. (2002) Coronary diameter in normal infants, children and patients with Kawasaki disease. *Pediatrics International*, **44**, 1–4.

Leung, D.Y., Cotran, R.S., Kurt-Jones, E., Burns, J.C., Newburger, J.W. & Pober, J.S. (1989) Endothelial cell activation and high interleukin-1 secretion in the pathogenesis of acute Kawasaki disease. *Lancet*, **2**, 1298–1302.

Maeno, N., Takei, S., Masuda, K., Akaike, H., Matsuo, K., Kitajima, I., Maruyama, I. & Miyata, K. (1998) Increased serum levels of vascular endothelial growth factor in Kawasaki disease. *Pediatric Research*, **44**, 596–599.

Maloney, J.P., Silliman, C.C., Ambruso, D.R., Wang, J., Tuder, R.M. & Voelkel, N.F. (1998) *In vitro* release of vascular endothelial growth factor during platelet aggregation. *American Journal of Physiology – Heart and circulatory physiology*, **275**, 1054–1061.

Möhle, R., Green, D., Moore, M.A., Nachman, R.L. & Rafii, S. (1997) Constitutive production and thrombin-induced release of vascular endothelial growth factor by human megakaryocytes and platelets. *Proceedings of the National Academy of Sciences of the United States of America*, **94**, 663–668.

Nadar, S., Blann, A.D. & Lip, G.Y. (2004) Platelet morphology and plasma indices of platelet activation in essential hypertension: effects of amlodipine-based antihypertensive therapy. *Annals of Medicine*, **36**, 552–557.

Newburger, J.W., Takahashi, M., Burns, J.C., Beiser, A.S., Chung, K.J., Duffy, C.E., Glode, M.P., Mason, W.H., Reddy, V. & Sanders, S.P. (1986) The treatment of Kawasaki syndrome with intravenous gamma globulin. *New England Journal of Medicine*, **315**, 341–347.

Nomura, Y., Masuda, K., Maeno, N., Yoshinaga, M. & Kawano, Y. (2004) Serum levels of interleukin-18 are elevated in the subacute phase of kawasaki syndrome. *International Archives of Allergy and Immunology*, **135**, 161–165.

Ohno, T., Igarashi, H., Inoue, K., Akazawa, K., Joho, K. & Hara, T. (2000) Serum vascular endothelial growth factor: a new predictive indicator for the occurrence of coronary artery lesions in Kawasaki disease. *European Journal of Pediatrics*, **159**, 424–429.

Onouchi, Y., Gunji, T., Burns, J.C., Shimizu, C., Newburger, J.W., Yashiro, M., Nakamura, Y., Yanagawa, H., Wakui, K., Fukushima, Y., Kishi, F., Hamamoto, K., Terai, M., Sato, Y., Ouchi, K., Saji, T., Nariai, A., Kaburagi, Y., Yoshikawa, T., Suzuki, K., Tanaka, T., Nagai, T., Cho, H., Fujino, A., Sekine, A., Nakamichi, R., Tsunoda, T., Kawasaki, T., Nakamura, Y. & Hata, A. (2008) ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. *Nature Genetics*, **40**, 35–42.

Papanas, N., Symeonidis, G., Maltezos, E., Mavridis, G., Karavageli, E., Vosnakidis, T. & Lakasas, G. (2004) Mean platelet volume in patients with type 2 diabetes mellitus. *Platelets*, **15**, 475–478.

Sato, Y. (1998) Transcription factor ETS-1 as a molecular target for angiogenesis inhibition. *Human Cell*, **11**, 207–214.

Storkebaum, E., Lambrechts, D. & Carmeliet, P. (2004) VEGF: once regarded as a specific angiogenic factor, now implicated in neuroprotection. *BioEssays*, **26**, 943–954.

Suzuki, A., Miyagawa-Tomita, S., Komatsu, K., Nishikawa, T., Sakomura, Y., Horie, T. & Nakazawa, M. (2000) Active remodeling of the coronary arterial lesions in the late phase of Kawasaki disease: immunohistochemical study. *Circulation*, **101**, 2935–2941.

Taki, M., Kobayashi, M., Ohi, C., Shimizu, H., Goto, K., Aso, K. & Murano, K. (2003) Spontaneous platelet aggregation in Kawasaki disease using the particle counting method. *Pediatrics International*, **45**, 649–652.

Terai, M., Honda, T., Yasukawa, K., Higashi, K., Hamada, H. & Kohno, Y. (2003) Prognostic impact of vascular leakage in acute Kawasaki disease. *Circulation*, **108,** 325–330.

Wallace, C.A., French, J.W., Kahn, S.J. & Sherry, D.D. (2000) Initial intravenous gammaglobulin treatment failure in Kawasaki disease. *Pediatrics*, **105,** 78.

Yasukawa, K., Terai, M., Shulman, S.T., Toyozaki, T., Yajima, S., Kohno, Y. & Rowley, A.H. (2002) Systemic production of vascular endothelial growth factor and fms-like tyrosine kinase-1 receptor in acute Kawasaki disease. *Circulation*, **105,** 766–769.

A Severe Form of Kawasaki Disease Presenting with Only Fever and Cervical Lymphadenopathy at Admission

Yuichi Nomura, MD, Michiko Arata, MD, Chihaya Koriyama, MD, Kiminori Masuda, MD, Yasuko Morita, MD, Daisuke Hazeki, MD, Kentaro Ueno, MD, Taisuke Eguchi, MD, and Yoshifumi Kawano, MD

Objective To examine the characteristics of patients with Kawasaki disease (KD) presenting with only fever and cervical lymphadenopathy at admission.

Study design The laboratory and clinical findings of patients with definite KD presenting with only fever and cervical lymphadenopathy at admission (KDiL) were compared with those of all other patients with KD.

Results Sixteen patients with KDiL (8.6%) and 171 patients without KDiL were examined. The patients with KDiL were significantly older (KDiL/non-KDiL: 4.9 ± 2.5/2.2 ± 1.9 years) and admitted earlier (3.0 ± 1.2/3.9 ± 1.3 days of illness) than the patients without KDiL. They also showed significantly elevated white blood cell counts and C-reactive protein levels. Patients with KDiL were treated with the same dose of intravenous immunoglobulin as the patients without KDiL but were treated slightly later and had significantly higher frequency of additional intravenous immunoglobulin treatment (38%/10%) and coronary artery abnormalities (25%/5%). After adjustment for age, white blood cell count, and day of illness at admission or first intravenous immunoglobulin administration, the presence of KDiL significantly increased the risk of being a nonresponder to IVIG treatment or development of a coronary artery abnormality.

Conclusions KDiL indicates a severe form of KD associated with increased risks of additional intravenous immunoglobulin treatment and coronary artery abnormalities. Patients with KDiL may require heightened surveillance and more aggressive treatment. *(J Pediatr 2010;■:■-■).*

See related article, p •••

As the number of patients with Kawasaki disease (KD) increases,[1] KD has become an important cause of acquired heart disease in children. To further reduce the prevalence of coronary artery abnormality (CAA) in KD, we need to determine optimum treatment strategies for high-risk patients. Screening of high-risk patients for CAA is a first step toward this end.

Many risk factors for CAA development have been reported.[2-5] Patients with KD with cervical lymphadenopathy as the dominant manifestation have significant risks for misdiagnosis, delay in KD treatment, and development of CAA.[6-8] Patients without KD presenting with only fever and cervical lymphadenopathy at admission (KD with isolated cervical lymphadenopathy, KDiL) may have similar risks. Consequently, characterization of patients with KDiL may help to reduce the incidence of CAA.

Methods

The study was approved by the Institutional Review Board at Kagoshima University Hospital. Informed consent was obtained from each child's parent before the treatment. The clinical records of consecutive patients with definite KD who were referred and then admitted to Kagoshima Medical Association Hospital between January 2001 and December 2007 were retrospectively reviewed. The diagnosis of KD was made using the Japanese criteria.[9] The patients were treated with aspirin and intravenous immunoglobulin (IVIG) (2 g/kg for 1 to2 days). Aspirin alone was given to patients with low Harada scores[2] (scores of 1 or 2) and patients who showed tendencies for peak body temperature to decrease on diagnosis. Patients who showed resolution

CAA	Coronary artery abnormality
CRP	C-reactive protein
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
KDiL	Kawasaki disease presenting with only fever and cervical lymphadenopathy at admission
LKD	Kawasaki disease presenting with only fever and cervical lymphadenopathy at presentation
OR	Odds ratio
Other-KD	Kawasaki disease that does not meet the LKD criteria
WBC	White blood cell
95% CI	95% Confidence intervals

From the Division of Pediatrics (Y.N., D.H., K.U., T.E., Y.K.) and the Division of Epidemiology and Preventive Medicine (C.K.), Kagoshima University Graduate School of Medical and Dental Sciences. Kagoshima, Japan; the Department of Pediatrics (M.A., K.M., Y.M.), Kagoshima Medical Association Hospital, Kagoshima, Japan

The authors declare no conflicts of interest.

 10.1016/j.jpeds.2009.11.042

Table I. Comparisons between patients with and without KDiL

	KDiL	Non-KDiL	*P* value
Number of cases [M/F]	16 [9/7]	171 [102/69]	
Age (y) (range)	4.9 ± 2.5 (0.5-9.2)	2.2 ± 1.9 (0.2-3.7)	<.001
Day of illness (range)			
At admission	3.0 ± 1.2 (1-6)	3.9 ± 1.3 (1-8)	.007
At diagnosis	5.1 ± 1.0 (4-7)	4.5 ± 1.1 (2-8)	.038
Number of clinical criteria besides fever (range)			
At admission	1.0 ± 0 (1)	4.1 ± 1.2 (0-5)	<.001
At the 5th day of illness	3.8 ± 1.4 (1-5)	4.3 ± 0.9 (0-5)	.018
Laboratory findings at admission (range)			
WBC ($\times 10^2/mm^3$)	195 ± 67 (98-307)	134 ± 43 (35-297)	<.001
Neutrophil (%)*	81 ± 8 (60-90)	62 ± 15 (18-89)	<.001
Hematocrit (%)	34.6 ± 6.5	34.1 ± 4.7	
Plt ($\times 10^4$ /mm^3)	29.7 ± 7.3 (19-43)	36.0 ± 10.9 (13-82)	.025
CRP (mg/dL)	11.5 ± 5.7 (5-24)	6.5 ± 4.4 (1-28)	<.001
Treatments and outcomes (range)			
IVIG (with/without)	16/0	158/13	
Day of illness at initial IVIG	5.3 ± 1.1 (4-7)	4.7 ± 1.2 (3-9)	.066
Initial IVIG dose (g/kg)	1.9 ± 0.3 (1.5-2.6)	1.8 ± 0.6 (1.9 ± 0.4)† (0-3.1)	
Additional IVIG	6 (38%)	17 (10%)	.0063
Duration of fever (days)	8.2 ± 3.2 (5-15)	6.2 ± 2.8 (1-16)	.009
Maximum *z*-score among the right or left coronary arteries			
At admission	1.4 ± 1.7 (-0.9-6.7)	1.1 ± 1.5 (-1.8-3.0)	.408
During the 1st month	3.5 ± 3.2 (0.8-11)	2.4 ± 2.4 (-0.4-14)	.090
At 1 month	2.7 ± 3.3 (-0.6-10)	1.4 ± 1.7 (-1.4-11)	.005
At 1 month >3.0	5 (31%)	19 (11%)	.038
CAA at 1 month	4 (25%)	8 (4.7%)	.012

Patients with KDiL, presenting with only fever and cervical lymphadenopathy at admission; WBC, white blood cell counts; Plt, platelet counts; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; Duration of fever, total fever days from the disease onset; CAA, coronary artery abnormality.
*Thirteen patients with KDiL and140 patients without KDiL.
†Not including patients who were treated with aspirin alone.

of fever (<37.5°C) within 48 hours of the initial IVIG were considered to be IVIG responders. Patients who did not meet the responder criteria were considered to be nonresponders and were given 1 or more additional IVIG treatments. Two-dimensional echocardiography was performed at the time of diagnosis and repeated after 1 or 2 days. It was subsequently performed several times a week during hospitalization or at an outpatient clinic. CAA were assessed using the *z*-score for coronary artery dimension, as described previously.[10] The maximum *z*-score among the scores for the right, left main, and left anterior descending arteries was used to evaluate CAA at admission and during the first month of illness. CAA was also determined clinically at 1 month of illness according to the criteria of the Japanese Ministry of Health and Welfare.[11] These criteria classify the coronary artery as abnormal when the internal lumen diameter is >3 mm in children under age 5 years or >4 mm in children age 5 years or older, when the internal diameter of any segment measures at least 1.5 times the diameter of an adjacent segment, or when the coronary artery lumen is clearly irregular.

Patients with KD were classified into 2 groups. Specifically, patients presenting with only fever and cervical lymphadenopathy (≥1.5 cm)[1] at admission were defined as patients with KDiL, and all other patients were defined as patients without KDiL. Consequently, the patients without KDiL included patients who did not present with cervical lymphadenopathy at admission and patients who presented with other clinical criteria in addition to cervical lymphadenopathy at admission, such as conjunctival injection and injected lips. The laboratory and clinical findings were compared between these 2 groups.

The mean values between patients with and without KDiL were compared using the Student *t* test. Fisher exact probability test was used to assess the frequencies in the 2 groups. The Mann-Whitney *U* test was used to compare the mean ranks between subsets of the patients with and without KDiL. To examine the risk factors for being a nonresponder and having CAA at 1 month of illness, logistic regression analyses were applied. In multivariate analyses, the presence of KDiL, age, white blood cell counts (WBC), and days of illness at admission (or at the first IVIG) were included in the models as covariates. The WBC and platelet counts at admission were categorized into tertiles, based on their distribution in patients with responses to IVIG or patients without CAA. A trend test was performed for logistic models using the raw data for each continuous variable. Maximum likelihood estimates of odds ratios (ORs) and the corresponding 95% confidence intervals (95% CI) were calculated. All *P* values presented are 2-sided, and values of $P < .05$ are considered statistically significant.

Results

During the study period, 187 patients were referred and then admitted to Kagoshima Medical Association Hospital and were eventually diagnosed as having definite KD. Among

Table II. Comparisons between patients with and without lymphadenopathy

Lymphadenopathy	With	Without	*P* value
Number of cases [M/F]	122 [76/46]	65 [35/30]	
Age (y)	2.8 ± 2.2	2.1 ± 1.4	<.001
Day of illness at admission	3.5 ± 1.1	4.3 ± 1.4	<.001
Laboratory findings at admission			
WBC ($\times 10^2$/mm^3)	144 ± 52	129 ± 41	.049
Plt ($\times 10^4$ /mm^3)	35.1 ± 10.4	36.1 ± 11.4	
CRP (mg/dL)	7.5 ± 4.9	5.7 ± 4.2	.015
Treatments and outcomes			
IVIG (with/without)	114/8	60/5	
Day of illness at the first IVIG administration	4.5 ± 1.0	5.1 ± 1.3	.002
Initial IVIG dose (g/kg)	1.8 ± 0.6	1.7 ± 0.7	
Additional IVIG	18 (15%)	3 (5%)	.050
Duration of fever (days)			
Total	6.6 ± 3.3	5.9 ± 1.9	
After IVIG	2.7 ± 3.3	1.5 ± 2.3	.008
Maximum *z*-score among the right and left coronary arteries			
At admission	1.0 ± 1.5	1.2 ± 1.5	
During the 1st month	2.6 ± 2.7	2.2 ± 2.1	
At 1 month	1.6 ± 2.1	1.2 ± 1.5	
CAA at 1 month	11 (9.0%)	1 (1.5%)	.060

WBC, white blood cell counts; Plt, platelet counts; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; Duration of fever, total fever days from the disease onset; CAA, coronary artery abnormality.

these, 16 patients showed only fever and cervical lymphadenopathy at admission (KDiL) and 171 patients did not meet KDiL criteria.

The characteristics of the patients with and without KDiL are shown in Table I. The patients with KDiL were significantly older and admitted earlier than the patients without KDiL. However, the patients with KDiL were diagnosed significantly later than the patients without KDiL. The number of clinical criteria at admission was significantly lower in the patients with KDiL than in the patients without KDiL. This difference became smaller on the 5th day of illness but was still significant. Many laboratory findings at admission differed significantly between the 2 groups. The patients with KDiL showed significantly elevated WBC, the proportion of neutrophils, and C-reactive protein (CRP) levels. The platelet counts were significantly lower in the patients with KDiL than in the patients without KDiL. The transaminases and albumin levels did not differ significantly between the 2 groups. Harada scores were significantly higher in the patients with KDiL than in the patients without KDiL (KDiL/non-KDiL: 4.3 ± 0.9/3.5 ± 1.4, $P = .042$).

All of the patients with KDiL and 92% of the patients without KDiL were treated with IVIG. The remaining 13 patients without KDiL (8%) were treated with aspirin alone; none of these patients showed CAA at 1 month of illness. The patients with KDiL were treated with the same dose of IVIG as the patients without KDiL but were treated slightly later than the patients without KDiL and showed significantly longer total fever days from the disease onset. The patients with KDiL also had a significantly higher frequency of additional IVIG treatment requirements than those without KDiL. Although the coronary *z*-scores at admission did not differ between the 2 groups, the maximum coronary *z*-scores during the first month of illness were greater in the patients with KDiL than in the patients without KDiL, although the differences were not significant. At 1 month of illness, the coronary artery dimension *z*-scores were significantly higher in the patients with KDiL than in those without KDiL. The incidence of patients with *z*-scores beyond 3 SD at 1 month of illness was significantly higher in the patients with KDiL than in the patients without KDiL. CAAs at 1 month of illness were observed in 4 patients with KDiL and 8 patients without KDiL, which was significantly different. None of the patients had development of a giant aneurysm.

The patients who had cervical lymphadenopathy during the disease course (65% of the total patients) were significantly older and had greater abnormalities in markers of systemic inflammation and a higher frequency of additional IVIG treatments compared with patients who did not have cervical lymphadenopathy (Table II). Among the 12 patients who had CAA at 1 month of illness, 11 had cervical lymphadenopathy.

Because the patients with KDiL were significantly older than the patients without KDiL, the older patients (above the mean age +1 SD of the patients without KDiL = 4.1 years of age) in the KDiL and non-KDiL groups were compared. The differences in the patient outcomes between the older patients in the KDiL (n = 10) and non-KDiL (n = 22) groups were similar to those in the entire cohort. Although the older patients with KDiL were given the same initial IVIG dose as the older patients without KDiL (1.9 ± 0.3 vs 1.9 ± 0.3 g/kg), 30% of the older patients with KDiL required additional IVIG treatment, whereas none of the older patients without KDiL did; this incidence was significantly different ($P = .024$). The incidence of CAA at 1 month of illness was significantly higher in the older patients with KDL than in the older patients without KDiL (30% vs 0%, $P = .024$).

Among the patients with early admission (before the mean admission day of illness in the patients without KDiL = the 4th day of illness), comparisons between the patients with and without KDiL (KDiL, n = 11; non-KDiL, n = 69) showed results similar to the comparisons of all the patients. The early-admitted patients with KDiL exhibited a significantly higher incidence of nonresponders than the early-admitted patients without KDiL (KDiL, n = 5, 45%; non-KDiL, n = 11, 16%, $P = .038$). The incidence of CAA at 1 month of illness was higher in the early-admitted patients with KDiL than in the early-admitted patients without KDiL, but the difference was not significant (KDiL, 2, 18%; non-KDiL, 7, 10%).

To investigate the risks for being a nonresponder and having a CAA at 1 month of illness, univariate logistic analyses were performed. The KDiL status, presence of cervical lymphadenopathy, early admission, days of illness at the first IVIG administration, and higher WBC and CRP levels at admission were found to be related to the risk of being a nonresponder (Table III). Except for early administration of the

Table III. **Results of univariate logistic regression analyses**

	Nonresponder			CAA at 1 month		
	No	Yes	OR (95% CI)	No	Yes	OR (95% CI)
Without KDiL	154	17	1.0 (reference)	163	8	1.0 (reference)
KDiL	10	6	5.4 (1.8-17)	12	4	6.8 (1.8-26)
Age (years)						
<1	44	10	1.0 (reference)	48	6	1.0 (reference)
1 – 2	75	4	0.2 (0.1-0.8)	77	2	0.2 (0.04-1.1)
3 –	45	9	0.9 (0.3-2.4)	50	4	0.6 (0.2-2.4)
	P for trend = .513			*P* for trend = .874		
Cervical lymphadenopathy						
Yes	102	20	4.1 (1.2-14)	111	11	6.3 (0.8-50)
No	62	3	1.0 (reference)	64	1	1.0 (reference)
Day of illness at admission						
<4	63	17	4.5 (1.7-12)	71	9	4.4 (1.1-17)
4 –	101	6	1.0 (reference)	104	3	1.0 (reference)
	P for trend = .034			*P* for trend = .008		
White blood cell counts at admission						
<117	57	3	1.0 (reference)	58	2	1.0 (reference)
117 –	56	5	1.7 (0.4-7.4)	58	3	1.5 (0.2-9.3)
148 –	51	14	5.2 (1.4-19)	59	6	2.9 (0.6-15)
	P for trend <.001			*P* for trend = .005		
Platelet counts at admission						
<31	54	11	1.0 (reference)	60	5	1.0 (reference)
31 –	56	3	0.3 (0.1-1.0)	58	1	0.2 (0.02-1.8)
39 –	54	9	0.8 (0.3-2.1)	57	6	1.3 (0.4-4.4)
	P for trend = .670			*P* for trend = .269		
CRP at admission						
<5	72	4	1.0 (reference)	72	4	1.0 (reference)
5 –	71	11	2.8 (0.8-9.2)	77	5	1.2 (0.3-4.5)
10 –	21	8	6.9 (1.9-25)	26	3	2.1 (0.4-9.9)
	P for trend = .002			*P* for trend = .137		
Day of illness at IVIG						
<5	60	14	1.0 (reference)	66	8	1.0 (reference)
5 –	91	9	0.4 (0.2-1.0)	97	3	0.3 (0.1-1.0)
	P for trend = .046			*P* for trend = .393		

IVIG, intravenous immunoglobulin; nonresponder, patient who did not respond to the first IVIG; CAA, coronary artery abnormality at 1 month of illness; OR, odds ratio; 95% CI, 95% confidence interval; KDiL, patients presenting with only fever and cervical lymphadenopathy at admission. iL, patients who did not meet the KDiL criteria.

first IVIG, these factors were also associated with the risk of having a CAA at 1 month of illness (Table III). Similar results were observed for the risk of a *z*-score beyond 3 SD at 1 month of illness (KDiL: OR = 3.6, 95% CI = 1.1 to 12; presence of cervical lymphadenopathy: OR = 1.3; 95% CI = 0.5 to 3.4).

The results of the multiple logistic regression analyses are shown in Table IV. The multivariate analyses always included age, a known risk factor for CAA, in the models. The KDiL status, higher WBC, and early initiation of IVIG were significantly related to the risk of being a nonresponder (Table IV). After adjustment for the effects of the WBC, days of illness at the first IVIG initiation, and age, the patients with KDiL showed a significantly increased risk of being a nonresponder (model 3 in Table IV). There were no significant interactions between patients with KDiL and the other clinical features for nonresponse. A marginally significant elevation of the risk of having a CAA at 1 month of illness was observed among the patients with KDiL, even after adjusting for the effects of WBC, days of illness at the first IVIG administration, and age (model 6 in Table IV). In addition, there was a significant interaction between the KDiL status and age ($P = .006$ using model 6 in Table IV). The risk for having a CAA tended to increase with age among the patients with KDiL, whereas the patients without KDiL showed an inverse association. Regarding the risk of a *z*-score beyond 3 SD at 1 month of illness, the presence of KDiL showed similar results to the risk for having a CAA (OR = 4.8, 95% CI = 1.1 to 20, using model 4; OR = 3.7, 95% CI = 0.8 to 17, using model 6).

Discussion

Cervical lymphadenopathy is the least common diagnostic criterion for KD and is present in approximately 42% to 65% of patients with KD.[9] It has already been reported that patients with KD with cervical lymphadenopathy as their dominant initial presentation show high incidences of CAA.[6-8] These patients are also significantly older and show greater abnormalities in markers of systemic inflammation, as do patients with KDiL. Consequently, these previous reports emphasize that avoidance of a delayed diagnosis of KD is important in such patients. The patients with KDiL in the present study were treated with IVIG on day 5.3 of illness on average (being 0.7 days later than the patients

Table IV. **Results of multiple logistic regression analyses**

Risk for being a nonresponder to intravenous immunoglobulin treatment			
	Model 1	**Model 2**	**Model 3**
KDiL			
No	1.0 (reference)	–	1.0 (reference)
Yes	13 (2.8-60)	–	8.9 (1.7-47)
WBC level at admission			
<117	–	1.0 (reference)	1.0 (reference)
117 –	–	1.7 (0.4-7.8)	1.6 (0.4-7.5)
148 –	–	4.6 (1.2-17)	3.8 (1.0-15)
P for trend		<.001	<.001
Day of illness at the first IVIG initiation			
<5	2.6 (1.0 -6.8)	2.5 (1.0-6.5)	2.8 (1.0-7.7)
5 –	1.0 (reference)	1.0 (reference)	1.0 (reference)
P for trend	.021	.029	.013
Risk of having a coronary artery abnormality at 1 month of illness			
	Model 4	**Model 5**	**Model 6**
KDiL			
No	1.0 (reference)	–	1.0 (reference)
Yes	8.5 (1.5-47)	–	6.7 (1.0-45)
WBC level at admission			
<117	–	1.0 (reference)	1.0 (reference)
117 –	–	1.5 (0.2-9.5)	1.3 (0.2-8.1)
148 –	–	2.3 (0.4-12)	1.6 (0.3-9.2)
P for trend		.019	.164
Day of illness at admission			
<4	3.5 (0.9-14)	3.5 (0.9-14)	3.0 (0.7-12)
4 –	1.0 (reference)	1.0 (reference)	1.0 (reference)
P for trend	.034	.020	.046

Factors included in the models
Model 1: Age, KDiL, and day of illness at the first IVIG initiation
Model 2: Age, WBC at admission, and day of illness at the first IVIG initiation
Model 3: Age, KDiL, WBC at admission, and day of illness at the first IVIG initiation
Model 4: Age, KDiL, and day of illness at admission
Model 5: Age, WBC at admission, and day of illness at admission
Model 6: Age, KDiL, WBC, and day of illness at admission

KDiL, patients presenting with only fever and cervical lymphadenopathy at admission; WBC, white blood cell counts; IVIG, intravenous immunoglobulin.

without KDiL). This delay does not seem sufficient to affect the outcomes compared with the previous reports, in which the first IVIG was given at 8.1 to 9.3 days of illness on average.[6-8] On the other hand, the early phase of treatment with IVIG is also a risk factor for requiring additional IVIG treatment or development of a CAA.[4,12,13] The patients with KDiL were admitted earlier than the patients without KDiL, but their IVIG treatments were not initiated earlier than those of the patients without KDiL. Therefore, the high proportion of nonresponders and CAA among the patients with KDiL may not be caused by delayed or early treatment but instead by their disease severity. The patients with KDiL showed greater abnormalities in markers of systemic inflammation, which are risks for requiring additional IVIG,[12,13] and these findings may explain why the patients with KDiL had a higher proportion of nonresponders and CAA.

The patients with cervical lymphadenopathy showed higher inflammatory marker levels and a higher proportion of nonresponders compared with the patients without lymphadenopathy. The presence of cervical lymphadenopathy may reflect the presence of more severe inflammation in patients with KD.

The patients with KDiL were older than those without KDiL, and their risk of having a CAA was found to increase with age. In older patients with KD, an association between a high incidence of cervical lymphadenopathy and CAA has been reported.[14,15] On the basis of these reports and the present study, KDiL may be an important reason for the risk of CAA in older patients with KD.

Kubota et al[16] reported that patients with KD presenting with only fever and cervical lymphadenopathy at presentation (patients with LKD) were older and admitted earlier than patients with KD with a common onset (other-KD). The CRP levels were significantly higher in the patients with LKD than the patients with other-KD, but the WBC did not differ between the patients with LKD and other-KD. The incidence of CAA was higher in the patients with LKD than in the patients with other-KD, but the difference was not significant. Among the total patients with KD, the incidence of patients with LKD was higher than the incidence of patients with KDiL (21% vs 9%). Because patients with LKD include those with KDiL, the similarities in these characteristics are not surprising. The difference in the outcomes may indicate that patients with KDiL comprise a severe subset of patients with LKD.

It is not easy to discriminate KDiL from bacterial lymphadenitis at admission. Tashiro et al[17] reported that ultrasonographic evaluation was useful during the diagnostic process among patients with KD with cervical lymphadenopathy and bacterial lymphadenitis. We have also reported useful risk factors to discriminate KDiL from lymphadenitis at admission (age >5.0 years; neutrophil count >10 000/mm^3; CRP >7.0 mg/dL; aspartate aminotransferase >30 IU/L).[18] The patients with KDiL had 2.7 risk factors on average at admission; 14 patients (88%) had 2 or more, and 2 patients had 1. These risk factors can help to prevent delays in KD diagnosis. The average interval between admission and the initial treatment day in patients with KDiL could be shortened by 2.3 days. It remains uncertain, however, whether this shortened interval would improve the prognosis, because the initial treatment for the patients with KDiL was only 0.7 days later from that for the patients without KDiL. Because this delay is very small, a new treatment strategy may be necessary for patients with KDiL. ■

Submitted for publication May 1, 2009; last revision received Oct 12, 2009; accepted Nov 13, 2009.

Reprint requests: Dr Yuichi Nomura, Division of Pediatrics, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima City, 890-8520 Japan. E-mail: uichi@m2.kufm.kagoshima-u.ac.jp.

References

1. Yanagawa H, Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K. Incidence of Kawasaki disease in Japan: the nationwide surveys of 1999-2002. Pediatr Int 2006;48:356-61.
2. Harada K. Intravenous gamma-globulin treatment in Kawasaki disease. Acta Pediatr Jpn 1991;33:805-10.
3. Zhang T, Yanagawa H, Oki I, Nakamura Y, Yashiro M, Ojima T, et al. Factors related to cardiac sequelae of Kawasaki disease. Eur J Pediatr 1999;158:694-7.
4. Nomura Y, Masuda K, Sameshima K, Yoshinaga M, Miyata K. Patients diagnosed as having Kawasaki syndrome within the 5th day of illness have a high risk of coronary artery aneurysm. Pediatr Int 2002;44:353-7.
5. Muta H, Ishii M, Sakaue T, Egami K, Furui J, Sugahara Y, et al. Older age is a risk factor for the development of cardiovascular sequelae in Kawasaki disease. Pediatrics 2004;114:751-4.
6. April MM, Burns JC, Newburger JW, Healy GB. Kawasaki disease and cervical adenopathy. Arch Otolaryngol Head Neck Surg 1989;115:512-4.
7. Stamos JK, Corydon K, Donaldson J, Shulman ST. Lymphadenitis as the dominant manifestation of Kawasaki disease. Pediatrics 1994;93:525-8.
8. Kao HT, Huang TC, Lin TY: Kawasaki disease presenting as cervical lymphadenitis or deep neck infection. Otolaryngol Head Neck Surg 2001;124:468-70.
9. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, et al. Revision of diagnostic guidelines for Kawasaki disease (5th revised edition). Pediatr Int 2005;47:232-4.
10. Kurotobi S, Nagai T, Kawakami N, Sano T. Coronary diameter in normal infants, children and patients with Kawasaki disease. Pediatr Int 2002;44:1-4.
11. Research Committee on Kawasaki Disease. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Tokyo, Japan: Ministry of Health and Welfare; 1994.
12. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr 2006;149:23740.
13. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 2006;113:2606-12.
14. Fan PC, Chiu CH, Yen MH, Huang YC, Li CC, Lin TY. School-aged children with Kawasaki disease: high incidence of cervical lymphadenopathy and coronary artery involvement. J Paediatr Child Health 2003;39:55-7.
15. Lee KY, Hong JH, Han JW, Lee JS, Lee BC, Burger D. Features of Kawasaki disease at the extreme of age. J Paediatr Child Health 2006;42:423-7.
16. Kubota M, Usami I, Yamakawa M, Tomita Y, Haruta T. Kawasaki disease with lymphadenopathy and fever as sole initial manifestations. J Paediatr Child Health 2008;44:359-62.
17. Tashiro N, Matsubara T, Uchida M, Katayana K, Ichiyama T, Furukawa S. Ultrasonographic evaluation of cervical lymph nodes in Kawasaki disease. Pediatrics 2002;109:e77.
18. Yanagi S, Nomura Y, Masuda K, Koriyama C, Sameshima K, Eguchi T, et al. Early diagnosis of Kawasaki disease in patients with cervical lymphadenopathy. Pediatr Int 2008;50:179-83.

Key words
川崎病
IgA 形質細胞
合成抗体
細胞質封入体
粘膜免疫

綜　説

川崎病の新しい病因論

IgA 免疫反応と細胞質封入体

三浦　大（みうら　まさる）*

要旨　川崎病の原因は不明であるが，遍在する病原体の感染が関与する可能性が高い．急性期川崎病の病理検体において，IgA 形質細胞の浸潤が冠動脈瘤，気管支などの組織に認められた．IgA の可変領域を基に合成した抗体によって，冠動脈瘤に浸潤したマクロファージの一部や気管支繊毛上皮細胞に関連抗原が検出された．最近，気管支繊毛上皮の抗原は蛋白質と RNA を含有する細胞質封入体であり，さらに非急性期の川崎病患者にも存在することが判明した．以上の所見は，未知の RNA ウイルスが経気道性に持続感染し，マクロファージを介して血行性に冠動脈などの標的臓器に伝播することにより，川崎病が発症することを示唆する．

はじめに

川崎病は乳幼児に好発する発熱性疾患で，血管炎による冠動脈瘤を合併し，日本のみならず先進国では小児の後天性心疾患の最大の原因となっている．その病因については多くの研究者が取り組んできたが，いまだに解明されていない．川崎病の発症予防，早期診断，より有効な治療法の開発のためにも，早期の病因究明が期待される．

米国の Rowley は，気管支繊毛上皮に感染した未知の RNA ウイルスが，IgA などの免疫系の活性化とマクロファージを介する標的臓器への感染を起こした結果，川崎病が発症するという独自の病因論を提唱している（**図 1**）[1)2)]．この理論は世界的に注目され，有名誌のレビュー[1)3)]や Rowley 自身が執筆した Nelson の教科書[2)]にも掲載されている．筆者は 2002 年から 2 年間同研究室で働く機会があり，その業績を日本語でまとめた[4)]．しかし，学会誌のため読者が限られており，その後に興味深いトピックも発表された．そこで，本稿では，最新の情報も交えて，改めて日本の小児科医に Rowley の病因論を紹介したい．

* 東京都立清瀬小児病院循環器科
〒 204-8597 東京都清瀬市梅園 1-3-1

I　川崎病の感染と免疫異常に関する従来の報告

はじめに従来の病因論を簡単に概説する[1)~3)]．川崎病の原因はまだ明らかではないが，何らかの感染の関与を示唆する幾つかの特徴を有する．まず，発生に季節性があり，ときに地域の流行がみられる．幼児期に好発することから，乳児期早期は母体からの移行抗体により防御され，成人は不顕性感染後に防御抗体を獲得するような，社会に広く遍在する病原体（ubiquitous agent）が疑われる．また，突然の発熱や発疹で発症し，数週間で自然軽快することも，一般的な感染症の経過に類似する．

従来の研究でも，種々のアプローチを用いて多くの感染症が川崎病の病因として提唱されてきたが（**表 1**），追試により否定されるという歴史を繰り返してきた[1)]．一時，黄色ブドウ球菌

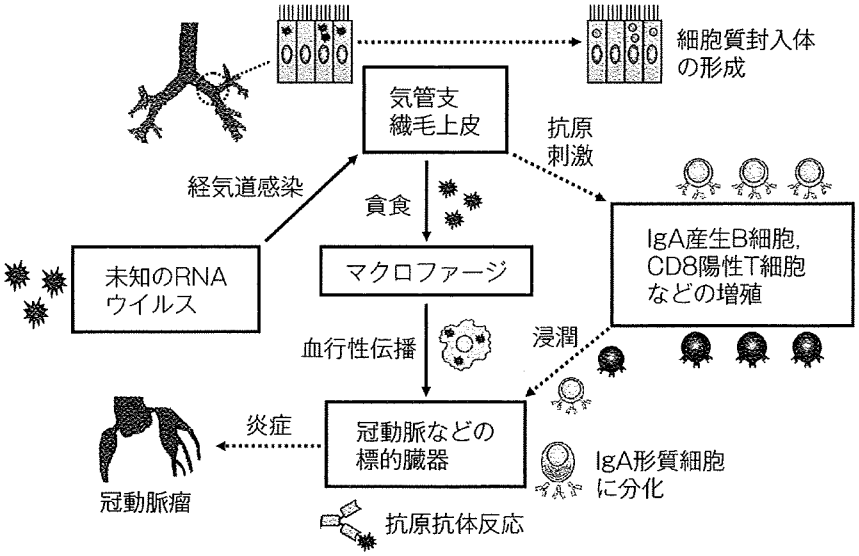

図1　Rowleyによる川崎病の病因論（三浦　大，2008[4]より改変）

未知の病原体（おそらくRNAウイルス）が中枢気管支の繊毛上皮細胞に感染し，周囲のリンパ節におけるIgA産生B細胞やT細胞のクローン性増殖を促す．マクロファージに取り込まれた病原体は，血行性に冠動脈などの標的臓器に到達する．組織に浸潤したIgA形質細胞，CD8陽性T細胞，マクロファージなどの働きで炎症が生じる．気管支繊毛上皮細胞では，病原体が細胞質封入体を形成し持続感染する．

表1　川崎病の病因の仮説

病原体
ウイルス
レトロウイルス（retrovirus）
EBウイルス（EB virus）
サイトメガロウイルス（cytomegalovirus）
コロナウイルス（coronavirus NL-63）
ボカウイルス（bocavirus）
未知の持続感染性RNAウイルス（previously unrecognized persistent RNA virus）
細菌
アクネ菌（*Propionibacterium acnes*）
レプトスピラ菌（*Leptospira* spp.）
サンギス菌（*Streptococcus sanguis*；口腔内αレンサ球菌の一種の旧名）
スーパー抗原となる細菌性毒素（toxic shock syndrome toxin-1などのbacterial toxin）
その他
リケッチア様病原体（*Rickettsia*-like agent）
非病原体
水銀（mercury）
カーペット用洗剤（rug shampoo）

（Rowley AH et al, 2008[1]より改変）

や化膿性レンサ球菌が産生する細菌毒素によるスーパー抗原説が注目された．しかし，否定的な報告も多く，前方視的な多施設共同研究では，川崎病群と発熱対照群とでスーパー抗原を産生する細菌の割合に有意差はなかった[5]．

川崎病では，免疫系が活性化し，種々の炎症細胞やサイトカインが顕著に増加する傾向がある．その炎症細胞の種類が末梢血と組織で異なる点も川崎病の特徴である[1]．末梢血では，炎症細胞は好中球，Tリンパ球はCD4陽性細胞が主体であるが，組織では，炎症細胞はマクロファージ，Tリンパ球はCD8陽性細胞が主体となる．腫瘍壊死因子（TNF）-α，インターロイキン（IL）-1，IL-6，IL-8をはじめとする多くのサイトカイン，ケモカインなどの異常もよく知られている[3]．

川崎病が日本をはじめとするアジア諸国に多く，家族内集積性がみられることからも，遺伝的な要素も関与していることは確実である．近年，サイトカインなど免疫機能に関する遺伝子多型性が次々と報告されている[6]．なかでも，T細胞の機能にかかわる *ITPKC*（1,4,5-trisphosphate 3-kinase C）遺伝子の多型性を示したOnouchiらの研究は価値が高い[7]．このように何らかの感染症が契機となり，遺伝的要因に基づく免疫異常によって全身性の血管炎が惹起された病態が川崎病であることは，ほぼ研究者のコンセンサスといえよう．

Ⅱ IgA形質細胞の浸潤と機序

Rowleyらは，1997年，通常はリンパ節や粘膜に存在するIgA形質細胞が川崎病の血管組織に浸潤していることを初めて報告した[8]．このような血管炎症候群は他に類をみず，川崎病の特徴的所見といえる．次いで，IgA形質細胞が気道・膵臓・腎臓などの臓器にも浸潤していることが判明した[9]．気道におけるIgA形質細胞の分布は，川崎病では中枢で著明であったが，RSウイルスやインフルエンザウイルス感染では末梢に目立った（**図2**）．

IgA形質細胞以外の炎症細胞では，冠動脈瘤組織においてCD8陽性T細胞，マクロファージ，樹状細胞などの浸潤が観察されている[10)11)]．川崎病の炎症の主役を担うマクロファージは，種々の炎症性サイトカインや細胞外マトリックス蛋白分解酵素（MMP）などを産生する．とくに組織での発現が観察されているMMP-2とMMP-9[12]は，膠原線維や弾性線維の断裂，血管壁の脆弱化から，冠動脈瘤の形成を促すと推測される．なお，マクロファージは膵臓にも浸潤し，IgA形質細胞とともに他臓器の炎症にも関与していると考える[13]．

種々の組織にIgA形質細胞が浸潤しているにもかかわらず，川崎病急性期では血液中のIgA産生B細胞数は少ない[14]．血液中のIgA産生B細胞は，冠動脈などの標的組織に選択的に移行し，形質細胞に分化すると推測される．免疫グロブリン療法終了後の血中IgA濃度の高値が冠動脈病変の独立した危険因子であるというMorikawaらの報告[15]は，このようなIgA産生B細胞の分布の変化に合致する．

IgA産生B細胞やマクロファージが血中から組織に浸潤する機序には，細胞接着分子が重要な役割を担うと予想される．われわれは，細胞接着分子のうちEセレクチンとVCAM-1（vascular cell adhesion molecule-1）が，川崎病冠動脈瘤の漿膜の新生血管に発現していることを報告した[16]．これらの細胞接着分子は，血管内皮増殖因子（vascular endothelial growth factor）などとともに[17]，冠動脈壁における血管新生により炎症の持続にも関与していると思われる．

Ⅲ 合成抗体の作製と抗原の検出

川崎病における免疫反応を惹起する抗原の種類を解明するため，川崎病の血管組織における

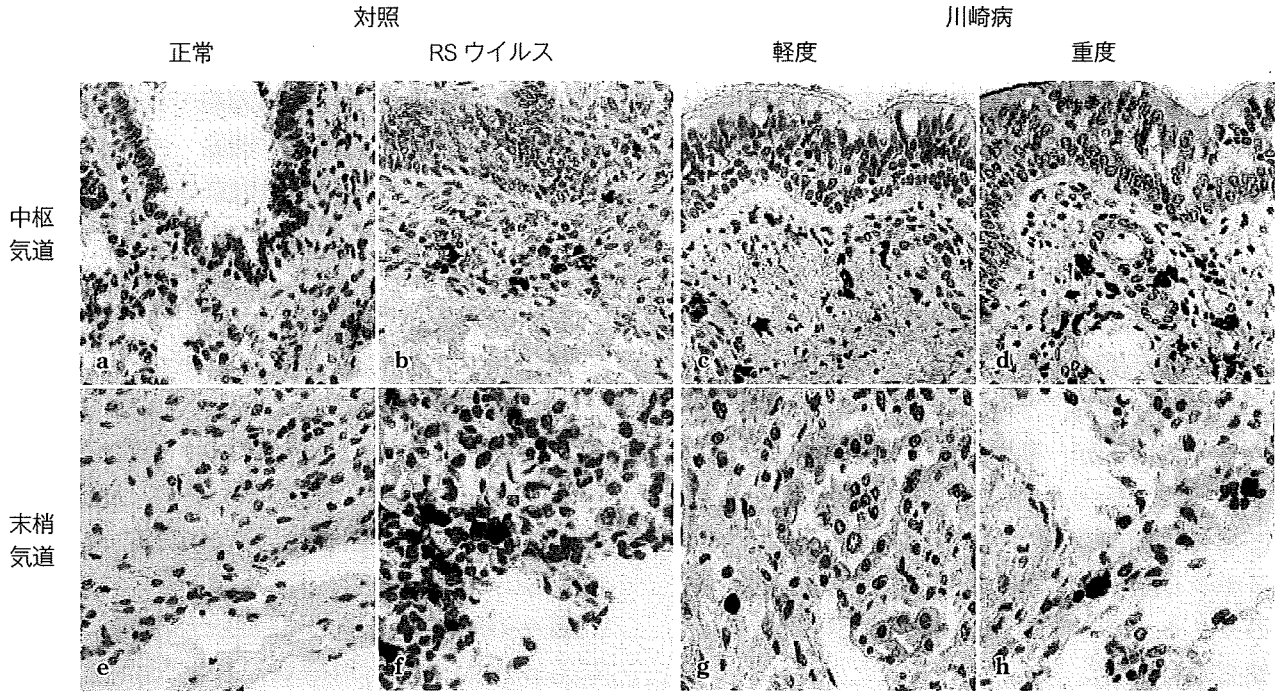

図 2　気道における IgA 形質細胞の免疫組織染色（Rowley AH et al, 2000[9]より改変）
中枢気道：IgA 形質細胞は，正常（a）ではなく，RS ウイルス肺炎（b）では少数認められる．川崎病では，軽度（c）から重度（d），浸潤している．
末梢気道：IgA 形質細胞は，正常（e）ではなく，RS ウイルス肺炎（f）では集積している．川崎病（g，h）では，中枢気道に比べ少数である．

IgA の α 鎖の相補性決定領域（CDR3）をコードする遺伝子の塩基配列が解析された[18]．CDR3 は oligoclonal なパターンを示したことから，スーパー抗原による非特異的反応ではなく，通常の抗原刺激による特異的な免疫反応と考えられた．

CDR3 の塩基配列をもとに合成抗体を作製し免疫組織染色を行ったところ，急性期川崎病の近位気管支繊毛上皮において，細胞質内抗原が高率に検出された（**図 3**）[19]．冠動脈瘤の組織に浸潤したマクロファージの一部でも抗原は陽性であった（**図 4**）．さらに，血管組織における α 鎖 CDR3 領域の検出頻度が高い塩基配列を用いた抗体は，検出頻度の低い塩基配列を用いた抗体に比べ，より強い抗原との結合性を示した[20]．

一般的な感染症と同様に，川崎病の病原体も気道だけでなく消化管から侵入する経路も想定される．しかし，われわれが行った検討では，川崎病の消化管組織における合成抗体による抗原検出率は，気管支に比し低値であった[21]．一部の陽性例でも，病原体の経消化管性の侵入部位である粘膜上皮やパイエル板では，抗原は検出されなかった（**図 5**）．したがって，川崎病の病原体は，経消化管性ではなく経気道性に侵入し，血行性に消化管に到達して炎症に関与すると考えた．

Ⅳ 細胞質封入体と RNA ウイルス持続感染

Rowley らは，透過型電子顕微鏡を用いて，川崎病の気管支繊毛上皮で検出される抗原は，均一な高電子密度の細胞質封入体であることを示した（**図 6**）[22]．この細胞質内封入体は，種々

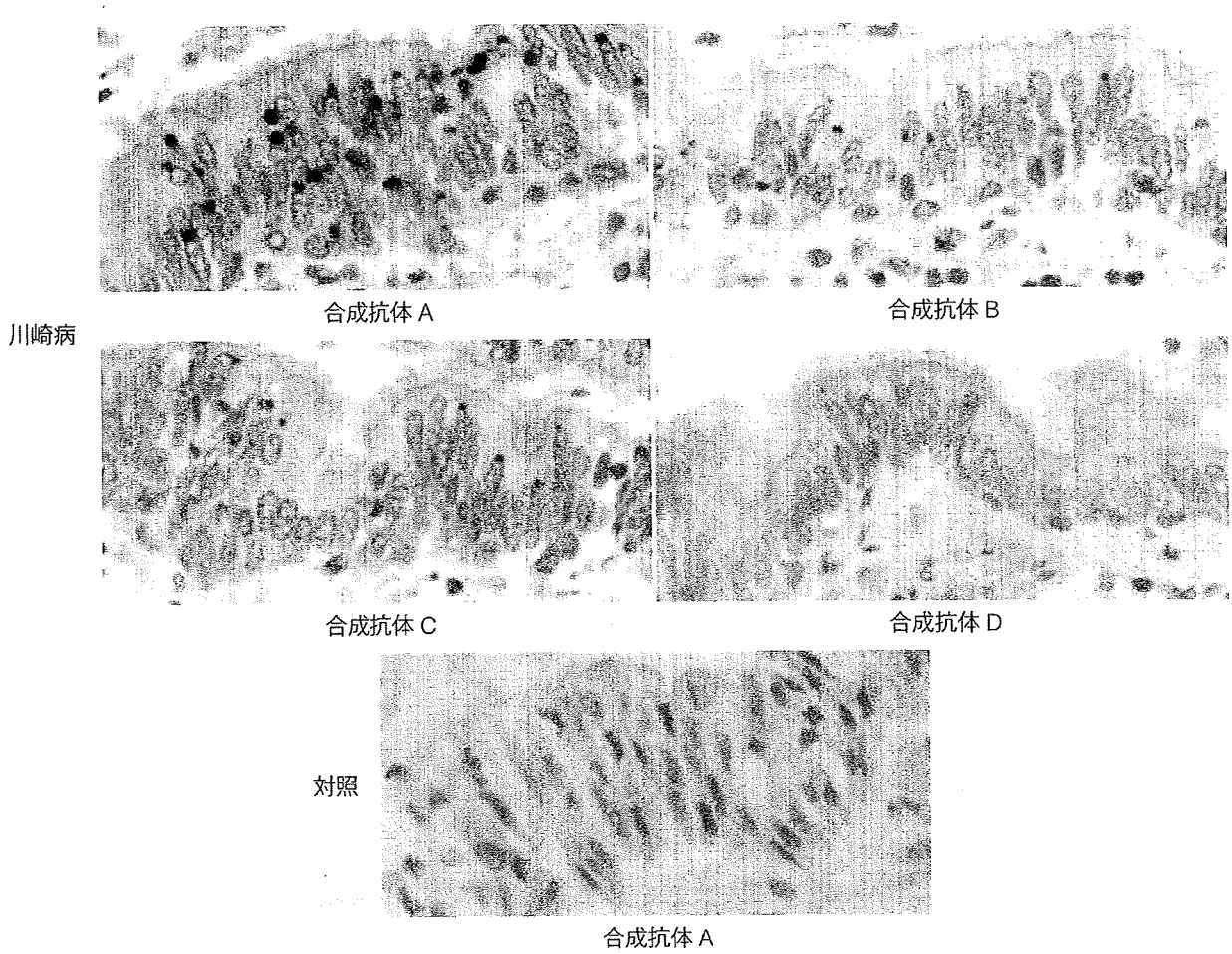

図3　川崎病の気管支繊毛上皮における細胞質封入体の免疫組織染色（Rowley AH et al, 2004[19]より改変）

合成抗体 A によって強く染色された細胞質封入体が，細胞の表面と核の間に認められる．合成抗体 B と C でもやや弱いが同様に染色されている．合成抗体 D では染色されない．対照の気管支繊毛上皮では，合成抗体 A の染色でも陰性である．

の染色所見から蛋白質と核酸を含むことも明らかにされた．細胞質封入体はパラミクソウイルスやレオウイルスが感染する際にも蛋白質と核酸が凝集して出現することから，川崎病のウイルス感染説を支持する所見といえる．

最近の報告によれば，気管支繊毛上皮の細胞質内封入体は，数カ月～数年経った非急性期の川崎病患者の 86%だけでなく，川崎病に罹患していない年長児・成人の対照患者の 26%にも認められた[23]．川崎病患者の肺，気管付属リンパ節，心筋では，合成抗体によって一部のマクロファージに抗原が検出された．さらに，核酸染色による検討では，細胞質封入体は DNA ではなく RNA に陽性であった．すなわち，川崎病の病原体は遍在する RNA ウイルスで，気管支繊毛上皮とマクロファージに持続感染するが，対照患者では不顕性感染すると推測された．

V Rowley の病因論の批判と展開

ここで病因論の解説から少し距離を置いて個人的な見解を述べる．Rowley らの研究をあえて批判すると，最大の限界はほとんどの対象が剖検例で免疫組織学的検討が主体であることと

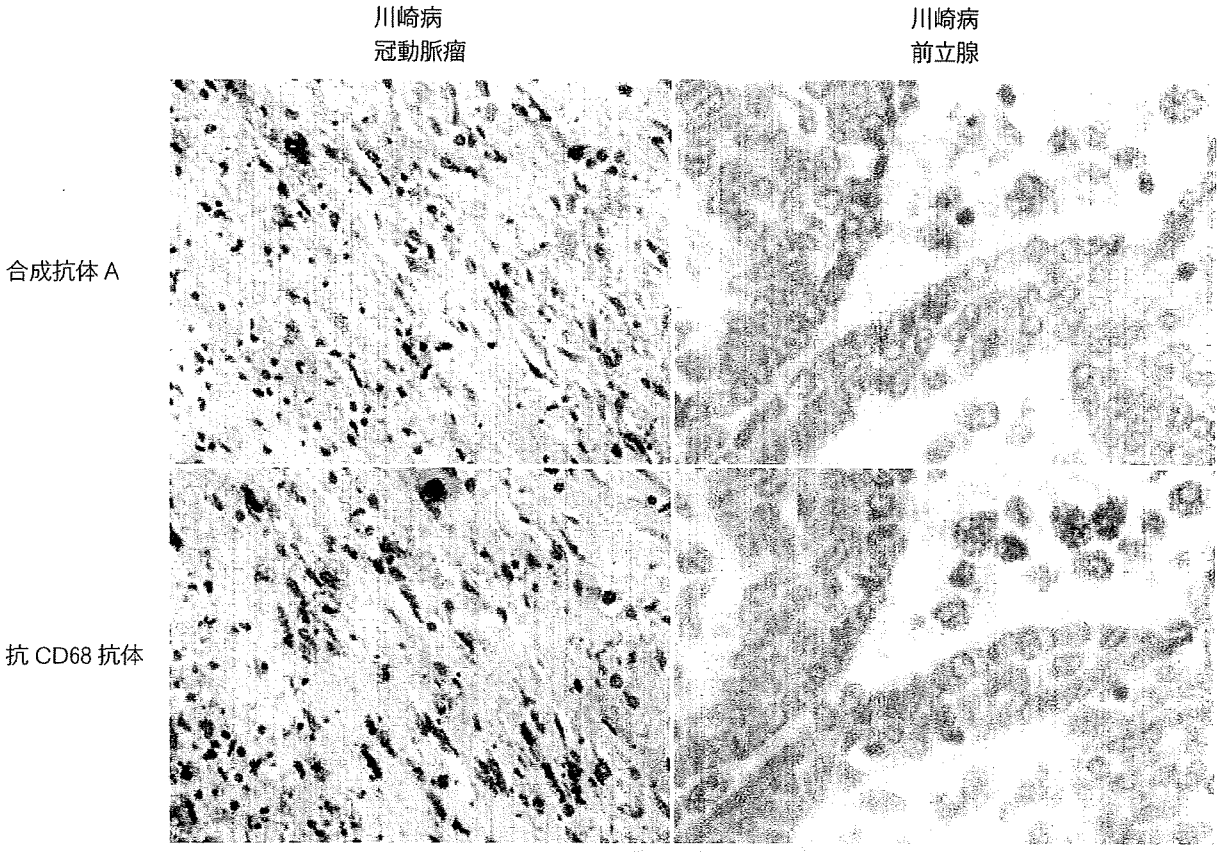

図4　川崎病の冠動脈瘤と前立腺管における隣接切片の免疫組織染色（Rowley AH et al, 2004[19]より改変）

冠動脈瘤の肥厚した内膜では，合成抗体 A に陽性の細胞と抗 CD68 抗体陽性のマクロファージが，同じ領域に多数浸潤している．前立腺管では，正常組織が指標となり，合成抗体 A の陽性細胞が CD68 にも陽性であることが，より明らかである．

思う．すなわち，きわめて重症な例のみを対象にしているわけで，通常の川崎病への検証は不十分であるといわざるを得ない．川崎富作先生も提案されていた生検組織の合成抗体による検討[24]は優れた着想であるが，実際の採取には相当の困難が伴う．

また，一部に日本人は含まれているが，多くは米国人の症例が対象である．今後，川崎病の病理検体を入手する機会があれば，適切な臓器（気管支，冠動脈を含む血管，心筋，リンパ節など）を種々の方法で保存し（そのままと OCT コンパウンドに入れた切片を液体窒素によって −70℃で凍結保存，およびグルタルアルデヒドとホルマリンに入れ室温保存），Rowley 研究室に提供すれば有意義な共同研究になるだろう．

Rowley の病因論で重要な IgA が粘膜免疫の主役を担うことは興味深い．筆者は，IgA と粘膜の免疫が幾つかの川崎病の特徴に合致すると考えている（**表2**）．第1に，川崎病の好発年齢である乳幼児期では，全身免疫より粘膜免疫が早く発達する．IgA レベルは血清中で低値の年齢でも，唾液中では高値を示す[25]．第2に，主要症状として充血の起こる眼球結膜・口唇・舌だけでなく，しばしば病変が及ぶ消化管・尿道・胆嚢はすべて粘膜に覆われている．病理学的に血管と同様に炎症をきたす外分泌腺（膵管，胆管，唾液腺など）[1)26]にも粘膜免疫が関与する．第3に，局所の抗原刺激で誘導された IgA 産

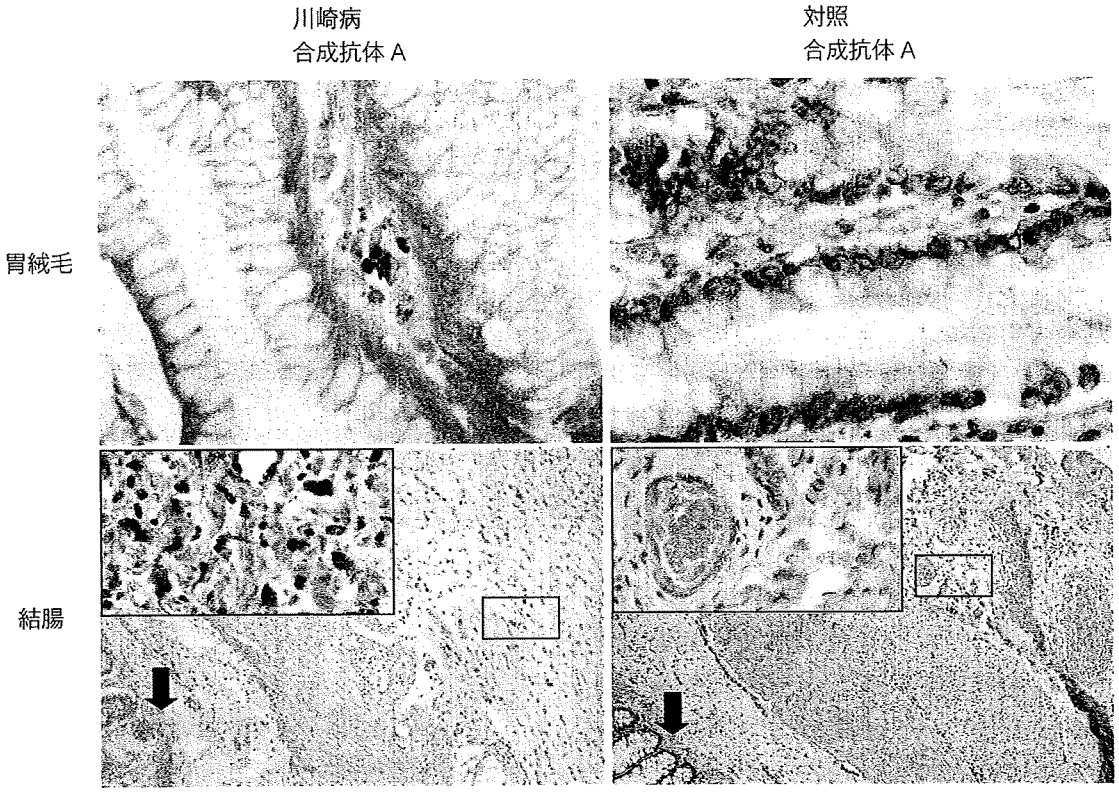

図5　川崎病の消化管の免疫組織染色（Miura M et al, 2005[21]より改変）
合成抗体 A による染色で，川崎病の 1 例では，胃の粘膜固有層の細胞質と結腸の漿膜に浸潤したマクロファージ様の細胞に，陽性の抗原が認められる．対照の同様の部位では陰性である．他の 1 例では腸間膜リンパ節内に検出された（図示していない）．病原体の経消化管性の侵入部位である粘膜上皮とパイエル板では，いずれも抗原を認めなかった．

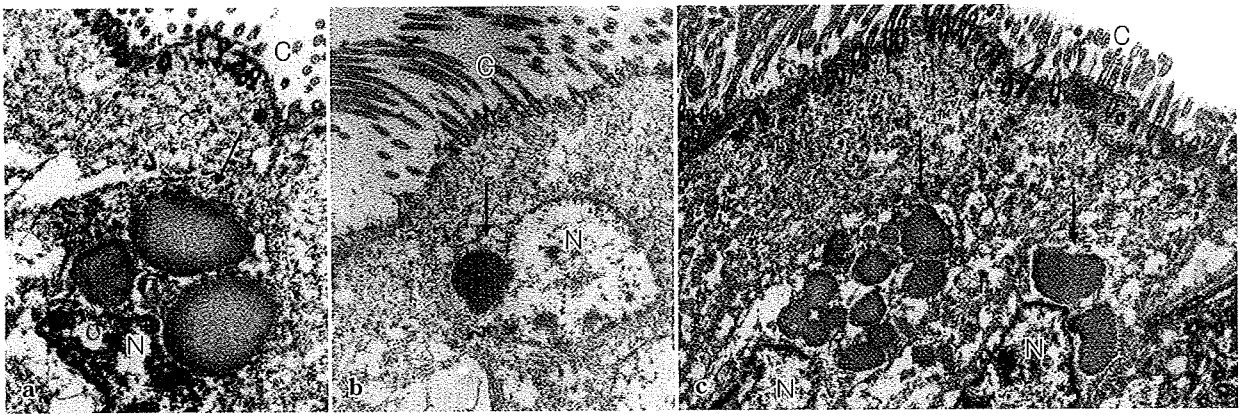

図6　川崎病の気管支繊毛上皮における細胞質封入体の電顕像（Rowley AH et al, 2005[22]より改変）
a：均一な高電子密度の細胞質封入体（矢印）が，繊毛（C）をもつ気管支上皮細胞の核（N）周囲に 3 つ認められる．
b：球状の細胞質封入体（矢印）が核に湾入している．
c：多数の細胞質封入体（矢印）が観察される．

表2　川崎病の特徴とIgA免疫系との関連

IgA形質細胞の組織への浸潤
川崎病の血管，気管支，膵臓などの組織にIgA形質細胞を多数認める．
血清IgA高値が冠動脈病変に関連
免疫グロブリン療法後の血清IgA高値が冠動脈病変の危険因子という報告がある．
乳幼児期に好発
IgAがつかさどる粘膜免疫は乳幼児期から発達する．
粘膜，外分泌腺の炎症
眼球結膜，口唇・口腔粘膜，尿道，胆道，膵臓などに炎症が起こる．
数日で全身に炎症が波及
抗原の侵入部位で誘導されたIgA産生B細胞は，共通粘膜免疫系を介し，全身の粘膜でIgA形質細胞に分化する．
Henoch-Schönlein紫斑病との合併例あり
小児の血管炎として代表的なHenoch-Schönlein紫斑病の発症にもIgAが関与するといわれている．
日本人に多発
IgA免疫疾患には人種差があり，日本ではIgA欠損症が少なく，IgA腎症が多い．

生B細胞が，さまざまな粘膜に帰巣し形質細胞に分化する共通粘膜免疫系（common mucosal immunity system）は，川崎病における急激な全身の粘膜の炎症を説明し得る．

粘膜免疫とは異なるが，川崎病と並ぶ小児の代表的血管炎であるHenoch-Schönlein紫斑病でも，IgA免疫異常が病因といわれており，川崎病との合併例も報告されている[27]．また，日本人では欧米人に比べ，IgA欠損症が少なく[28] IgA腎症が多い[29]ことから，川崎病と同様のIgA免疫系の人種差が示唆される．

Rowley自身は，粘膜免疫の川崎病における役割には否定的で，IgA免疫に基づく合成抗体は抗原の検索に利用したにすぎないと述べ，未知のRNAウイルス感染説を強調している（私信）．実際，IgGとIgMの形質細胞も川崎病の血管組織に浸潤していることと（IgA形質細胞より少ない）[8]，IgA欠損症と川崎病の合併例の報告は[30]，IgA以外の免疫系も発症に影響していることを意味する．しかしながら，IgAのつかさどる粘膜免疫は川崎病の特徴に合致する部分が多く，従来ほとんど検討されていないことから，病因研究の新しい方向性かもしれないと筆者は考えている．

おわりに

IgA形質細胞の血管組織への浸潤を出発点とし，合成抗体によって気管支繊毛上皮の細胞質封入体を検出し，未知のRNAウイルスの持続感染説にたどりついた，約10年間のRowleyの軌跡を紹介した．現状では，Rowleyが唱える川崎病の発症のメカニズムは[1)2)]，以下のように要約することができる（図1）．

① 未知のRNAウイルスが気管支繊毛上皮に感染する．

② 気管付属リンパ節でIgA産生B細胞とCD8陽性T細胞などのクローン性増殖が起こる．

③ 病原体はマクロファージに貪食され，血行性に冠動脈や外分泌腺などの標的臓器に伝播する．

④ IgA産生B細胞やCD8陽性T細胞が組織に浸潤し，分化した形質細胞からIgAが分泌され，抗原抗体反応により炎症が生じる．

⑤ 病原体は気管支繊毛上皮で細胞質封入体を形成し持続感染する．

本綜説によって，世界的に知られている川崎病の新しい病因論の理解が深まり，さらに将来の病因研究の一助になれば幸いである．

文献

1) Rowley AH et al：Searching for the cause of Kawasaki disease-cytoplasmic inclusion bodies provide new insight. Nat Rev Microbiol 2008；6：394-401
2) Rowley AH, Shulman ST：Kawasaki disease. In；Behrman RE et al (ed), Nelson Textbook of Pediatrics. 18th ed, Saunders, 2007：1042-1046
3) Burns JC, Glodé MP：Kawasaki disease. Lancet 2004；364：533-544
4) 三浦 大：川崎病急性期におけるIgA免疫反応と合成抗体を用いた関連抗原の検出．日本小児循環器学会雑誌 2008；24：3-10
5) Leung DYM et al：Prevalence of superantigen-secreting bacteria in patients with Kawasaki disease. J Pediatr 2002；140：742-746
6) 山岸敬幸：ポストゲノム時代の川崎病の病因・病態論．日本小児循環器学会雑誌 2007；23：126-130
7) Onouchi Y et al：ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat Genet 2008；40：35-42
8) Rowley AH et al：IgA plasma cells in vascular tissue of patients with Kawasaki syndrome. J Immunol 1997；159：5946-5955
9) Rowley AH et al：IgA plasma cell infiltration of proximal respiratory tract, pancreas, kidney, and coronary artery in acute Kawasaki disease. J Infect Dis 2000；182：1183-1191
10) Brown TJ et al：CD8 T lymphocytes and macrophages infiltrate coronary artery aneurysms in acute Kawasaki disease. J Infect Dis 2001；184：940-943
11) Yilmaz A et al：Activated myeloid dendritic cells accumulate and co-localize with $CD3^+$ T cells in coronary artery lesions in patients with Kawasaki disease. Exp Mol Pathol 2007；83：93-103
12) Gavin PJ et al：Systemic arterial expression of matrix metalloproteinases 2 and 9 in acute Kawasaki disease. Arterioscler Thromb Vasc Biol 2003；23：576-581
13) Miura M et al：Macrophage infiltration of pancreatic acini and islets in acute Kawasaki disease. Pediatr Infect Dis J 2003；22：1106-1108
14) Shingadia D et al：Surface and cytoplasmic immunoglobulin expression in circulating B-lymphocytes in acute Kawasaki disease. Pediatr Res 2001；50：538-543
15) Morikawa Y et al：Coronary risks after high-dose gamma-globulin in children with Kawasaki disease. Pediatr Int 2000；42：464-469
16) Miura M et al：Cell adhesion molecule expression in coronary artery aneurysms in acute Kawasaki disease. Pediatr Infect Dis J 2004；23：931-936
17) Freeman AF et al：Angiogenesis in fatal acute Kawasaki disease coronary artery and myocardium. Pediatr Cardiol 2005；26：578-584
18) Rowley AH et al：Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. J Immunol 2001；166：1334-1343
19) Rowley AH et al：Detection of antigen in bronchial epithelium and macrophages in acute Kawasaki disease by use of synthetic antibody. J Infect Dis 2004；190：856-865
20) Rowley AH et al：Cloning the arterial IgA antibody response during acute Kawasaki disease. J Immunol 2005；175：8386-8391
21) Miura M et al：Detection of Kawasaki disease-associated antigen in inflamed gastrointestinal tract in acute Kawasaki disease. Pediatr Infect Dis J 2005；24：927-929
22) Rowley AH et al：Cytoplasmic inclusion bodies are detected by synthetic antibody in ciliated bronchial epithelium during acute Kawasaki disease. J Infect Dis 2005；192：1757-1766
23) Rowley AH et al：RNA-Containing Cytoplasmic Inclusion Bodies in Ciliated Bronchial Epithelium Months to Years after Acute Kawasaki Disease. PLoS ONE 2008；3：e1582
24) 川崎富作：日本川崎病研究センターニュースレター 2006；11：1
25) Weemaes C et al：Development of immunoglobulin A in infancy and childhood. Scad J Immunol 2003；58：642-648
26) Amano S et al：General pathology of Kawasaki disease. Acta Pathol Jpn 1980；30：681-694
27) Miura M et al：A case of Kawasaki disease accompanied by Henoch-Schönlein purpura. Clin Exp Rheumatol 2004；22：377-378
28) 二上由紀ほか：日本人のIgA欠損献血者のHLA抗原．日本輸血学会雑誌 2002；48：298-303
29) 石倉健司：小児IgA腎症．小児内科 2009；41：196-199
30) Nishikawa T et al：Selective IgA deficiency complicated by Kawasaki syndrome. Pedaitr Int 2008；50：816-838

急性期治療

ウリナスタチン療法

佐地 勉

KD：Kawasaki disease

IVIG：intravenous immunoglobulin

UTI：ulinastatin

＊1
ウイルスの不活化法として60℃，10時間以上の液状加熱処理および多孔性中空糸膜によるナノフィルトレーションを施した液状製剤である（昭和60年4月承認）．HIV，HCV，HBVはPCRで陰性が確認されている[2]．

HIV：human immunodeficiency virus

HCV：hepatitis C virus

HBV：hepatitis B virus

＊2
肝，腎，膵，肺，心，副腎，胃，大腸，脳，精巣．

＊3
これらの内因性UTIは全身性炎症性疾患（LPSによる敗血症）で臓器保護的に作動していることが，UTIノックアウトマウスで明らかとなっている（Inoue K, et al. Mol Pharmacol 2005；67：673-80.）．

LPS：lipopolysaccharide（リポ多糖）

＊4
その他の副作用
肝機能異常（0.5％），白血球減少（0.2％），発疹，瘙痒感などの過敏症状（0.1％），下痢（0.1％），血管痛（0.1％）など．

ERCP：endoscopic retrograde cholangiopancreatography（内視鏡的逆行性膵胆管造影）

＊5
使用注意事項として，IVIG製剤との同一ルートの混注は避けるべきである．

DIC：disseminated intravascular coagulation（播種性血管内凝固症候群）

AML：acute myelogenous leukemia（急性骨髄性白血病）

＊6
実験的にもショックモデルで有効性が確認されている．

◎急性期川崎病（KD）の治療の基本は主に免疫グロブリン超大量静注療法（IVIG）であるが，一部に不応例・抵抗例が存在する．それに対する二次選択薬の一つとしてウリナスタチン（UTI）＊1（ミラクリッド®）がoff-labelで使用されてきた．症例報告からは臨床上の有用性が推測できるが，絶対評価には計画された臨症試験が必要である[1]．

性状と適応症

◎UTIはヒト尿性（human urinary）trypsin inhibitorで，ヒトの尿から高度精製され，trypsinをはじめとする種々のタンパク融解酵素（膵酵素）に対して阻害作用を有する分子量67,000（理論上は24,000）の多価酵素阻害薬（セリンプロテアーゼインヒビター）である．由来は血中のinter-α-trypsin inhibitorであると考えられている．全身諸臓器＊2で産生が確認されている＊3．

◎治療薬としてのUTIの適応症は，①膵炎初期，②急性循環不全の2つの疾患群であるが，適応外として他にも有効な疾患群が報告されている（❶）．

主な作用と副作用（②）

◎5,000 IU/kg/回，3～6回/日（1回は50,000 IUを超えない）で使用されることが多い．主にタンパク分解，浮腫，壊死，出血による血管病変の軽減化に作用する．半減期は，30万IU/10 mL静注で40分である．

◎重大な副作用はアナフィラキシーショック＊4．①薬剤に過敏症の既往歴の患者，②過敏性素因患者，③過去にUTI投与を受けた患者，④ゼラチン含有製剤に対し過敏症のある患者，には禁忌である＊5．

❶ ウリナスタチンの適応疾患とoff-labelとして有用な疾患

適応疾患

1. 急性循環不全（出血性・細菌性・外傷性・熱傷性ショック）における循環動態の改善（10万IU，1～3回/日 静注，点滴静注）
2. 急性膵炎（術後，外傷性，ERCP後），慢性再発性膵炎の急性増悪期（膵炎初期：2.5万～5万IU，1～3回/日 点滴静注，以降漸減）

適応外＊6 off-label使用の報告

1. 炎症性疾患：川崎病，血管性紫斑病，Stevens-Johnson症候群，慢性関節リウマチ，肺アスペルギルス症
2. 消化器疾患：潰瘍性大腸炎，肝切除後肝障害
3. 腎疾患：腎機能障害，シスプラチン腎障害，溶血性尿毒症症候群
4. 婦人科疾患：切迫早産（頸管中コラーゲン分解抑制），子宮収縮抑制，絨毛羊膜炎，子宮頸管炎，膣炎，双胎間輸血症候群，羊水塞栓症
5. ショック：体外循環後循環不全，熱傷，癌転移抑制，外科手術周術期管理，出血性ショック，肺・冠動脈虚血再灌流障害
6. 血液疾患：DIC，AML，造血器腫瘍性疾患，ベルオキシダーゼ陽性白血病

作用機序

TNF-α 抑制作用

- 多くのサイトカイン抑制に関与する．冠動脈や肺手術後の再灌流障害では，UTI は多核白血球からのエラスターゼ，TNF-α，IL-6，IL-8 の遊離を抑え，結果的に再灌流障害を抑える．
- また TNF-α により活性化される血管内皮細胞（EC）上の ICAM-1 の発現を抑制し，EC 保護機能がある．
- UTI の TNF-α 産生抑制作用は単球からの産生か分泌を抑制するのに対し，メシル酸ガベキサート（Gabexate mesilate）は NFκB の活性化を強く抑制する[3]．

好中球エラスターゼ阻害作用，細胞活性化抑制作用*7

- UTI は，とくに好中球からのエラスターゼの放出阻害と放出後の不活化の両方に作用し，結果的に酸素ラジカルの除去，サイトカイン・接着分子の活性を低下させる．
- ライソゾーム膜の安定化作用により各種のタンパク分解酵素の遊離を抑制する．たとえば TNF-α を含む心筋抑制因子や毒性因子の遊離阻害作用，凝固阻害作用，EC 成長促進などの作用もある．その他，報告されている多彩な生物学的作用の機序をまとめて列記する（❷）．
- 川崎病以外で好中球エラスターゼの産生亢進状態がある一部の病態に対して有用性を示している．

川崎病での作用点

- 急性期 KD*8 では，好中球により誘導・分泌されたエラスターゼの不活化だけでなく，好中球に直接作用してエラスターゼの産生・分泌を抑制し，内皮細胞障害を防御する[3]．好中球での PGH_2 と TXA_2 の mRNA の亢進を抑制する．
- 1990 年代には症例報告が相次いだ．その結果として，①軽症例での単独の効果，②併用による IVIG の減量効果，③IVIG 無効例・不応例・抵抗例，および再燃例への有効性，が考えられた．
- CRP 値や白血球の増加が少ない軽症例では，時に IVIG を使用せずアスピリン（ASA）との併用でも治療が可能である*9．
- UTI を第一選択薬として用いた場合，57％（5,000 IU/kg×6）～74％（50,000 IU×6）は UTI 使用後の IVIG を必要としなかった（IVIG 回避例）．また IVIG との併用により，重症例やいわゆるハイリスク例では IVIG の使用量を減少させているとする報告がある[4]・*10．
- ほとんどの施設では急性期の第一選択薬として IVIG を用いているが，15～20％に存在する不応例に対し UTI を代替治療薬の一つとして位置づけている施設もある．

❷ ウリナスタチンの生物学的作用

1. 種々のタンパク分解酵素（プロテアーゼ）の阻害
   trypsin＞α-kimotrypsin＞N-elastase＞N-cathepsin G＞plasmin＞P-elastase＞Hyaluronidase＞lipase＞amylase＞enterokinase
2. 炎症性サイトカイン産生抑制
   IL-1α, IL-1β, IL-6, IL-8, TNF-α, 接着分子
3. NFκB 伝達経路阻止作用
4. 好中球・マクロファージ・血小板の活性化抑制，エラスターゼ遊離/活性酸素産生抑制，細胞障害抑制
5. ライソゾーム膜安定化
6. 実験的炎症（肺，肝，腎，膵）やショックの軽減
7. 細胞外マトリックス形成抑制
8. 内皮細胞障害軽減（好中球による）

IL：interleukin，TNF：tumor necrosis factor（腫瘍壊死因子），NFκB：nuclear factor kappa B.

*7
薬効のエビデンスは RCT で 8 論文であり，臓器障害 OR：0.45，肝障害 0.53 である．
（村田宣夫. Therapeutic Research 2006；27：599-601.）

*8
急性期 KD に対する UTI の最初の使用報告例は，1993 年の岡田（山形大）の報告と思われる（岡田昌彦ほか．日児誌 1993；97：43-8.）．

PGH_2：prostaglandin H_2

TXA_2：thromboxane A_2

ASA：aspirin

*9
また IVIG 投与や再投与後の再燃例，さらに IVIG にまったく反応しない症例や，いわゆる不応例にも時に有効であるという意見が多い．

*10
岐阜県立多治見病院の中野らは 1990 年代前半より UTI を併用した治療で，半数以上に効果があり，IVIG 使用量を減少できると推測している．