Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Serum Tenascin-C as a Novel Predictor for Risk of Coronary Artery Lesion and Resistance to Intravenous Immunoglobulin in Kawasaki Disease

– A Multicenter Retrospective Study –

Yoshiaki Okuma, MD; Kenji Suda, MD, PhD; Hideyuki Nakaoka, MD; Yasuhiro Katsube, MD, PhD; Yoshihide Mitani, MD, PhD; Yukako Yoshikane, MD, PhD; Fukiko Ichida, MD, PhD; Takeji Matsushita, MD; Hiroyuki Shichino, MD; Isao Shiraishi, MD, PhD; Jun Abe, MD, PhD; Michiaki Hiroe, MD, PhD; Toshimichi Yoshida, MD, PhD; Kyoko Imanaka-Yoshida, MD, PhD

Background: Tenascin-C (TN-C) is an extracellular matrix glycoprotein that is heavily upregulated at sites of inflammation. We conducted a retrospective study to assess the utility of TN-C as a novel biomarker to predict the risk of developing coronary artery lesions (CAL) and resistance to intravenous immunoglobulin (IVIG) in patients with Kawasaki disease (KD).

Methods and Results: We collected blood samples of 111 KD patients (IVIG-responder: 89, IVIG-resistant: 22; CAL: 8) and 23 healthy controls, and measured the serum levels of TN-C. TN-C levels on admission were significantly higher in patients than in healthy controls and in patients during convalescence after IVIG administration (69.6 vs. 20.4 vs. 39.7 ng/ml, respectively; P<0.001), and correlated positively with C-reactive protein (P<0.001), neutrophil (percentage; P=0.005), and ALT (P<0.001), and negatively with platelet count (P=0.023) and sodium level (P=0.025). On admission, TN-C levels in patients who later developed CAL were significantly higher than in those without CAL (P=0.010), and significantly higher in IVIG-resistant subjects than in IVIG-responders (P=0.003). The accuracy of TN-C testing for the prediction of IVIG resistance was comparable to that of the Kobayashi score.

Conclusions: Serum TN-C could be a biomarker for predicting the risk of developing CAL and IVIG resistance during the acute phase of KD. (*Circ J* 2016; **80:** 2376–2381)

Key Words: Biomarkers; Coronary artery lesions; Intravenous immunoglobulin (IVIG) resistance; Kawasaki disease; Tenascin-C

Kawasaki disease (KD) is an acute febrile illness of childhood characterized by systemic vasculitis of unknown origin.[1] Coronary artery lesions (CAL) constitute the most critical complication of KD and can lead to myocardial infarction (MI) and death or chronic distress in adulthood. High-dose intravenous immunoglobulin (IVIG) therapy can subdue the inflammation in KD and reduce the occurrence of CAL.[2–4] However, approximately 20% of KD patients show resistance to a single course of IVIG therapy.[5] Many studies have shown that these IVIG-resistant patients have a greater risk of CAL.[6–8] Currently, several scoring systems that combine multiple clinical parameters are used to

Received June 9, 2016; revised manuscript received September 7, 2016; accepted September 25, 2016; released online October 15, 2016 Time for primary review: 48 days

Department of Pediatrics (Y.O., T.M., H.S.), Department of Cardiology (M.H.), National Center for Global Health and Medicine, Tokyo; Course of Advanced and Specialized Medicine, Juntendo University Graduate School of Medicine, Tokyo (Y.O., H.S.); Department of Pediatrics and Child Health, Kurume University School of Medicine, Kurume (K.S.); Department of Pediatrics, Faculty of Medicine, University of Toyama, Toyama (H.N., F.I.); Department of Pediatrics, Nippon Medical School, Tokyo (Y.K.); Department of Pediatrics (Y.M.), Department of Pathology and Matrix Biology (T.Y., K.I.-Y.), Mie University Graduate School of Medicine, Tsu; Department of Pediatrics, Faculty of Medicine, Fukuoka University, Fukuoka (Y.Y.); Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Osaka (I.S.); Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo (J.A.); and Mie University Research Center for Matrix Biology, Tsu (T.Y., K.I.-Y.), Japan

Mailing address: Yoshiaki Okuma, MD, Department of Pediatrics, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan. E-mail: yokuma@hosp.ncgm.go.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-16-0563

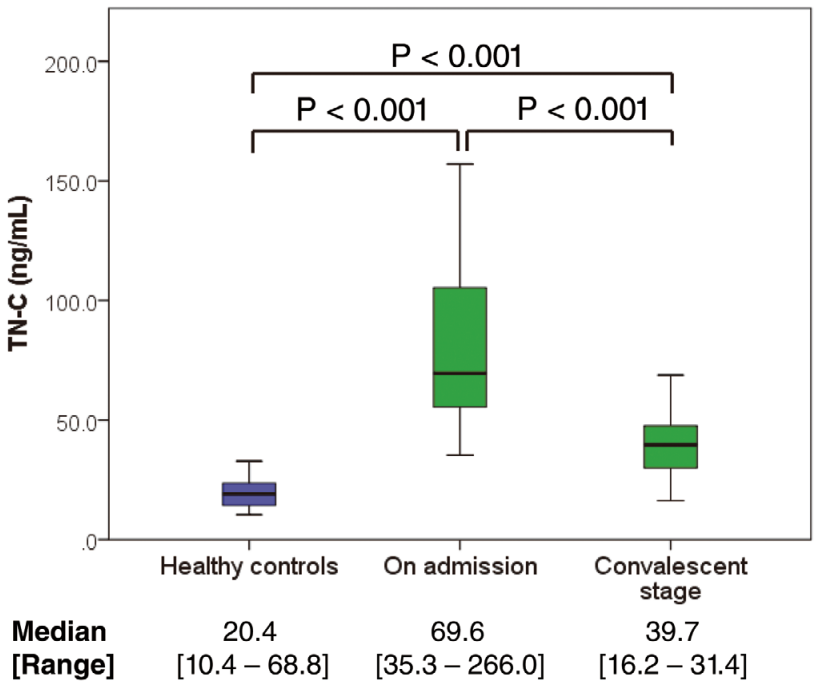

Figure 1. Serial changes in tenascin-C (TN-C) levels in Kawasaki disease (KD) patients (n=68) and healthy controls (n=23). Serum levels were high on admission, but significantly decreased during the convalescent stage after intravenous immunoglobulin therapy in the KD patients.

predict IVIG resistance that could lead to the development of CAL.[9–13] Because the accuracy of these systems has not been high in other countries,[14] and they are cumbersome, a novel simple biomarker to predict the risk of CAL is required.

Tenascin-C (TN-C) is an extracellular matrix glycoprotein that is sparse in normal tissue, but upregulated at sites of tissue injury and inflammation.[15–17] It has diverse functions in the regulation of cell behavior and tissue remodeling in many developmental and pathological processes.[18–20] A growing number of studies have reported that serum TN-C is elevated in various cardiovascular diseases and can be used as a biomarker for the diagnosis of disease activity, as well as a predictor of outcome in patients with aortic aneurysm/dissection,[21,22] MI,[23] and dilated cardiomyopathy.[15,16,24,25] The aim of this study was to determine whether serum TN-C could be used as a biomarker to predict the development of CAL and IVIG resistance in patients with acute KD.

Table 1. Correlation Between Serum TN-C Level and Other Laboratory Data

	n	Correlation coefficient	P value
CRP	104	0.369	<0.001
WBC	62	–	0.761
% Neutrophils	92	0.287	0.005
Platelets	98	−0.229	0.023
Albumin	58	–	0.165
T-bilirubin	56	–	0.078
AST	96	–	0.119
ALT	68	0.451	<0.001
Sodium	93	−0.232	0.025

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; TN-C, tenascin-C; WBC, white blood cells.

Methods

Subjects

We conducted a multicenter retrospective study and enrolled 111 KD patients and 23 age- and sex-matched healthy controls. Frozen serum samples from KD patients were collected from the following participating institutions: National Center for Global Health and Medicine, Toyama University, Mie University, and Kurume University. Frozen serum samples from healthy controls were collected from Nippon Medical School Musashikosugi Hospital. All KD patients fulfilled the criteria for the Diagnostic Guidelines for Kawasaki Disease.[26] Each patient received 2 g/kg of IVIG over 24 h and 30–50 mg/kg/day of aspirin within 7 days of onset. The aspirin dosage was decreased to 5 mg/kg/day after patients became afebrile. We assessed the coronary arteries by 2D echocardiography before treatment and at least twice weekly thereafter. CAL were diagnosed if an examination showed an internal lumen diameter ≥3 mm in children less than 5 years old and ≥4 mm in children 5 years or older; if the internal diameter of a given segment was at least 1.5-fold larger than that of an adjacent segment; or if the lumen appeared irregular. IVIG resistance was defined in cases of patients needing second-line therapy.

This study was approved by the Research Ethics Committee at each collaborative institution. Informed consent for the use of samples was given by participants or their parents/guardians.

Measurement of Serum TN-C Levels

Blood samples were obtained from 111 KD patients on admission and from 68 of them while convalescing (after 25 days of illness and C-reactive protein (CRP) normalization; day 1 was defined as the first day of fever). The age- and sex-matched 23 healthy controls served the purpose of comparison. Blood samples were sent to the National Center for Global Health and

Table 2. Characteristics and Data Comparison of IVIG-Responder and IVIG-Resistant Groups of Patients With Kawasaki Disease

	IVIG-responder group	IVIG-resistant group	P value
n	89	22	
Age, months	24 [2–84]	21 [4–72]	0.742
Male, n (%)	48 (53.9)	10 (45.5)	0.476
Laboratory data before IVIG			
TN-C, ng/ml	69.6 [28.8–266.0] (n=89)	114.0 [35.3–653.4] (n=22)	0.003
WBC, $\times 10^3/\mu l$	13.7 [6.9–28.0] (n=52)	11.6 [6.1–16.9] (n=10)	0.053
Neutrophils, %	70 [25–93] (n=77)	78 [38–87] (n=15)	0.269
Platelets, $\times 10^4$/ml	33.0 [18.9–83.1] (n=83)	26.9 [20.7–57.6] (n=15)	0.051
CRP, mg/dl	8.6 [1.1–30.7] (n=86)	10.5 [3.0–18.7] (n=18)	0.036
Albumin, g/dl	3.6 [2.3–4.9] (n=49)	3.8 [3.1–4.1] (n=9)	0.846
T-bilirubin, mg/dl	0.5 [0.3–2.4] (n=47)	0.7 [0.5–4.5] (n=9)	0.034
AST, IU/L	36 [16–801] (n=81)	62 [28–1,441] (n=15)	0.023
ALT, IU/L	35 [6–272] (n=52)	80 [7–764] (n=10)	0.206
Sodium, mEq/L	135 [125–141] (n=79)	134 [130–139] (n=14)	0.332

Data are shown as median [range]. IVIG, intravenous immunoglobulin. Other abbreviations as in Table 1.

Table 3. Characteristics and Data Comparison of CAL(–) and CAL(+) Groups of Patients With Kawasaki Disease

	CAL(–) group	CAL(+) group	P value
n	103	8	
Age, months	24 [2–84]	20 [4–55]	0.315
Male, n (%)	54 (52.4)	4 (50.0)	0.590
IVIG resistance, n (%)	17 (16.5)	5 (62.5)	0.007
Laboratory data before IVIG			
TN-C, ng/ml	70.3 [28.8–266.0] (n=103)	139.3 [55.5–653.4] (n=8)	0.010
WBC, $\times 10^3/\mu l$	12.7 [6.1–28.0] (n=58)	9.8 [6.9–16.7] (n=4)	0.295
Neutrophils, %	70 [25–93] (n=87)	78 [46–91] (n=5)	0.297
Platelets, $\times 10^4$/ml	33.0 [18.9–83.1] (n=92)	26.8 [20.7–35.0] (n=6)	0.032
CRP, mg/dl	8.7 [1.1–30.7] (n=97)	10.7 [8.3–17.5] (n=7)	0.064
Albumin, g/dl	3.7 [2.3–4.9] (n=54)	3.4 [3.2–3.8] (n=4)	0.322
T-bilirubin, mg/dl	0.6 [0.3–4.5] (n=53)	1.6 [0.6–2.0] (n=3)	0.114
AST, IU/L	38 [16–801] (n=90)	44 [29–1,441] (n=6)	0.586
ALT, IU/L	34 [6–535] (n=58)	249 [56–764] (n=4)	0.008
Sodium, mEq/L	135 [125–141] (n=88)	134 [129–136] (n=5)	0.189

Data are shown as median [range]. CAL, coronary artery lesions. Other abbreviations as in Tables 1,2.

Medicine where serum TN-C was measured by enzyme-linked immunosorbent assay using the Human TN-C Large (FN lll-C) Assay Kit (Immuno-Biological Laboratories Co, Gunma, Japan). Medical, demographic, and laboratory data on admission were collected in all cases.

Statistical Analysis

All analyses were performed with SPSS software version 20 (SPSS Japan, Tokyo, Japan) and R ver. 3.1.0. Data are presented as median with the range for continuous variables, or as a percentage of the patients in a given categorical variable. A series of group comparisons were conducted using the t-test for numerical data of normal distribution, the Mann-Whitney U test for data that did not have normal distribution, and the Fisher exact and chi-square tests for categorical data. Comparisons of TN-C levels between admission and convalescence were performed with the Wilcoxon's signed rank test. Correlations between TN-C levels and other laboratory data were determined by Spearman's correlation coefficients. To compare the power of predicting IVIG resistance based on serum TN-C and Kobayashi score, receiver-operating characteristic curves were plotted and the areas under the curves (AUC) were calculated. We compared the predictive accuracy of the 2 models by DeLong test. All P values were 2-tailed; $P<0.05$ was considered statistically significant.

Results

Serum TN-C Levels in the Acute Phase of KD

The change in TN-C levels between admission and convalescence was evaluated for 68 of 111 patients (Figure 1). Their TN-C levels on admission were significantly higher than those of the healthy controls ($P<0.001$) and significantly decreased during convalescence after IVIG administration ($P<0.001$). TN-C levels correlated positively with both CRP ($P<0.001$) and the percentage of neutrophils ($P=0.005$), and negatively

with platelet count (P=0.023); however, the correlation coefficients were not high (Table 1). We also compared TN-C levels with other laboratory parameters involved in risk scoring for KD.[10,11,13] TN-C levels correlated positively with alanine aminotransferase (ALT; P<0.001) and negatively with sodium (P=0.025) levels. There was no correlation with white blood cell count, or total bilirubin, albumin, and aspartate aminotransferase (AST) levels.

Serum TN-C Levels in IVIG-Responder and IVIG-Resistant Patients

We compared the TN-C levels on admission of IVIG-responders (n=89) with those of IVIG-resistant patients (n=22). Serum TN-C levels were significantly higher in the IVIG-resistant patients than in the IVIG-responders (P=0.003; Table 2). Significant differences in CRP (P=0.036), total bilirubin (P=0.034), and AST (P=0.023) were also found between the 2 groups.

Comparison of Predicting IVIG Resistance by TN-C and Kobayashi Score

IVIG resistance were predicted by receiver-operating characteristics curve analysis of TN-C levels in 83 cases comparing with the Kobayashi score.[11] For predicting IVIG resistance, a TN-C cut-off value of 95.2 ng/ml yielded a sensitivity of 58%, specificity of 78%, a positive predictive value of 30%, and a negative predictive value of 92%. We also compared these 2 models and the percentage of IVIG-resistant cases in the high-risk group (Kobayashi score >5 points, n=18) were significantly higher than that of the low risk group (Kobayashi score <5 points, n=65) (9.1% vs. 33.3%, respectively, P=0.019). The AUC of TN-C was comparable to that of the Kobayashi score (AUC 0.607 vs. 0.667, respectively; P=0.607).

Serum TN-C Levels in Patients With and Without CAL

We compared the laboratory data of patients with CAL [CAL(+) group, n=8] and without [CAL(–) group, n=103]. TN-C levels in the CAL(+) group were significantly higher than in the CAL(–) group (P=0.01; Table 3). Significant differences between the CAL(+) and CAL (–) groups were also seen in platelet counts (P=0.032) and ALT levels (P=0.008). Moreover, the rate of IVIG resistance was significantly higher in the CAL(+) group than in the CAL(–) group (P=0.007). No significant differences in CRP, total bilirubin and AST levels were found between the 2 groups. For predicting CAL formation by TN-C level on admission, a TN-C cut-off value of 113.3 ng/ml yielded a sensitivity of 63%, specificity of 84%, a positive predictive value of 23%, and a negative predictive value of 97% with an AUC of 0.77 (95% confidence interval 0.59–0.96, P=0.01). Coronary angiography of a representative patient with high serum TN-C on admission and who eventually developed giant coronary aneurysm is shown in Figure 2.

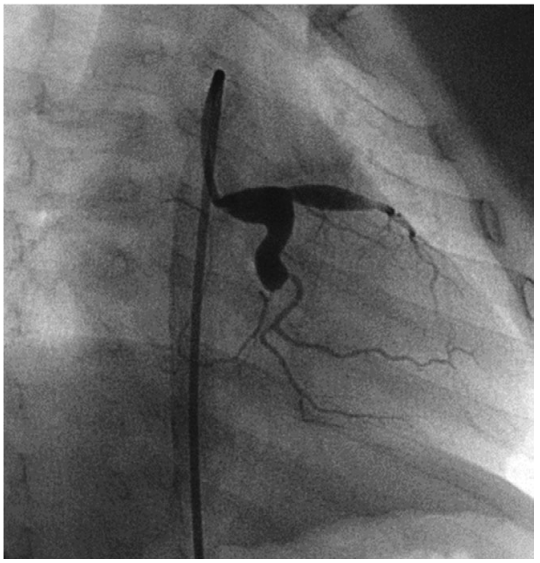

Figure 2. Coronary angiogram from a representative case, a 4-month-old boy, with a coronary artery lesion. Laboratory data showed increased serum levels of tenascin-C (371 ng/ml) and C-reactive protein (17.5 mg/dl). The patient was resistant to the initial course of intravenous immunoglobulin infusion and was febrile for 19 days.

Discussion

The results of this study indicated that the serum TN-C level might be a useful biomarker to predict the risk of developing CAL and IVIG resistance in the acute phase of KD. The accuracy of the prediction of IVIG resistance was comparable to that of the Kobayashi score,[11] which is the most common risk scoring technique currently used. TN-C levels on admission were significantly higher in patients who later developed CAL than in patients who did not, and were significantly higher in IVIG-resistant patients than in IVIG-responders. Furthermore, serum TN-C levels on admission predicted the development of CAL and IVIG resistance with high accuracy. Recent advances in therapeutic strategies have provided additional treatment options, such as IVIG plus prednisolone,[12] for patients at high risk of CAL; therefore, risk stratification of KD patients is a critical step. Several parameters, including the duration of fever,[27–29] and the levels of vascular endothelial growth factor,[30,31] B-type natriuretic peptide,[32] serum albumin,[33] serum sodium,[34] CRP,[35] platelet-neutrophil aggregates,[36] and inflammatory cytokines, including tumor necrosis factor-α and interleukin-6,[35,37] are reported to predict the development of CAL. To improve the diagnostic accuracy for predicting IVIG resistance and CAL formation in KD patients, several clinical risk scoring systems have been developed using a combination of multiple patient profiles and laboratory parameters.[10,11,13] The Kobayashi score[11] in particular is often used in Japan to predict IVIG resistance. A recent study reported that the addition of prednisolone to initial IVIG treatment reduces the incidence of CAL in high-risk KD patients according to the Kobayashi score.[12] However, a recent North American cohort generated controversy regarding the use of risk scores.[14] Therefore, a novel and simple biomarker for risk stratification is necessary. In the present study, we have shown that the accuracy of predicting IVIG resistance via serum TN-C levels was comparable to that of the Kobayashi score, suggesting that serum TN-C alone could be a biomarker to identify high-risk patients.

TN-C could be a marker of inflammatory activity in KD, because it is generally upregulated in inflammatory lesions and regulates inflammatory cell responses.[17,38,39] Recently, elevated serum levels of TN-C were reported to reflect local expression and are used as biomarkers for disease activity in pediatric patients with various inflammatory diseases,[40–42] as well as in adults.[15,16] In this study, we found that the serum TN-C levels of KD patients were elevated in the acute stage and the levels correlated with known inflammatory markers, such as percentage of neutrophils and CRP level, although the correlation coefficients were not high. In a mouse KD model, vascular

lesions expressed TN-C, and expression correlated with the severity of inflammation.[43] Therefore, serum TN-C levels in KD patients could reflect inflammatory activity in CAL.

TN-C could be involved in the process of CAL formation and/or vascular remodeling in KD. Analyses of several disease models have shown that the major sources of TN-C in vascular disease are medial smooth muscle cells and fibroblasts, especially myofibroblasts.[15,16] Various proinflammatory cytokines and growth factors, in addition to mechanical stress, upregulate TN-C expression. Transforming growth factor-β, one of the key modulators of KD arteritis,[44] is also known to induce TN-C expression. TN-C acts as an autocrine/paracrine factor on smooth muscle cells, fibroblasts, and macrophages.[16,38,45] For example, in a mouse model of aortic aneurysm/dissection, TN-C is produced by vascular smooth muscle cells under strong humoral and mechanical stress, and protects the vascular wall by modulating inflammatory and fibrotic responses during pathological tissue remodeling.[46] Although the exact roles of TN-C in the cascade leading to CAL formation have yet to be elucidated, TN-C could be a novel marker of not only inflammation but also pathological tissue remodeling.

Study Limitations

First, the sample size might not be large enough to determine CAL and IVIG-resistance predictors. However, the frequency of IVIG resistance (20/111, 19.8%) was comparable to data from the National Registry,[5] and reflected the general features of patients with KD. Second, the retrospective nature of this study prevented us from collecting complete data sets and precluded the use of multivariate logistic regression analysis to identify laboratory data predictive of IVIG resistance and increased risk of CAL. The frequency of CAL (8/111, 7.2%) was somewhat higher than in the National Registry data,[5] perhaps because our samples were obtained from severe KD cases admitted to collaborative tertiary care institutions. A larger scale prospective study is therefore needed.

In conclusion, the serum level of TN-C may be a promising new biomarker for predicting the risk of CAL and IVIG resistance in patients during the acute phase of KD. Early identification of IVIG resistance could help to prevent CAL through the addition of other antiinflammatory medicines to initial IVIG therapy.

Acknowledgments

We thank Mayumi Iwasaki and Chihiro Eguchi for measuring the serum levels of TN-C, and Kiyoshi Matsuoka, MSc for the statistical analyses. T.Y. receives royalties on TN-C antibodies from Immuno-Biological Laboratories Co, Japan. Part of this study was presented at The Association for European Pediatric and Congenital Cardiology (AEPC 2013).

Funding

This work was supported by grants from the National Center for Global Health and Medicine (23D114), the Japanese Therapeutic Study Group for Kawasaki Disease (JSGK 2013) to Y.O., and grants for intractable disease from the Ministry of Health, Labour and Welfare of Japan (201128212, 201324121, 20145052) and a grant for Kawasaki Disease Research from Japan Blood Products Organization to K.I.-Y.

References

1. Burns JC, Glode MP. Kawasaki syndrome. *Lancet* 2004; **364:** 533–544.
2. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984; **2:** 1055–1058.
3. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991; **324:** 1633–1639.
4. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986; **315:** 341–347.
5. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, et al. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: From the results of the 22nd nationwide survey. *J Epidemiol* 2015; **25:** 239–245.
6. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease: US/Canadian Kawasaki Syndrome Study Group. *Pediatr Infect Dis J* 1998; **17:** 1144–1148.
7. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, Nana A, Prachuabmoh C, Kangkagate C. Immunoglobulin failure and retreatment in Kawasaki disease. *Pediatr Cardiol* 2003; **24:** 145–148.
8. Uehara R, Belay ED, Maddox RA, Holman RC, Nakamura Y, Yashiro M, et al. Analysis of potential risk factors associated with nonresponse to initial intravenous immunoglobulin treatment among Kawasaki disease patients in Japan. *Pediatr Infect Dis J* 2008; **27:** 155–160.
9. JCS Joint Working Group. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2013): Digest version. *Circ J* 2014; **78:** 2521–2562.
10. 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:** 237–240.
11. 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:** 2606–2612.
12. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): A randomised, open-label, blinded-endpoints trial. *Lancet* 2012; **379:** 1613–1620.
13. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr* 2007; **166:** 131–137.
14. Sleeper LA, Minich LL, McCrindle BM, Li JS, Mason W, Colan SD, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr* 2011; **158:** 831–835. e833.
15. Imanaka-Yoshida K. Tenascin-C in cardiovascular tissue remodeling: From development to inflammation and repair. *Circ J* 2012; **76:** 2513–2520.
16. Imanaka-Yoshida K, Yoshida T, Miyagawa-Tomita S. Tenascin-C in development and disease of blood vessels. *Anat Rec (Hoboken)* 2014; **297:** 1747–1757.
17. Midwood KS, Hussenet T, Langlois B, Orend G. Advances in tenascin-C biology. *Cell Mol Life Sci* 2011; **68:** 3175–3199.
18. Chiquet-Ehrismann R, Orend G, Chiquet M, Tucker RP, Midwood KS. Tenascins in stem cell niches. *Matrix Biol* 2014; **37:** 112–123.
19. Giblin SP, Midwood KS. Tenascin-C: Form versus function. *Cell Adh Migr* 2015; **9:** 48–82.
20. Spenle C, Saupe F, Midwood K, Burckel H, Noel G, Orend G. Tenascin-C: Exploitation and collateral damage in cancer management. *Cell Adh Migr* 2015; **9:** 141–153.
21. Nozato T, Sato A, Hikita H, Takahashi A, Imanaka-Yoshida K, Yoshida T, et al. Impact of serum tenascin-C on the aortic healing process during the chronic stage of type B acute aortic dissection. *Int J Cardiol* 2015; **191:** 97–99.
22. Nozato T, Sato A, Hirose S, Hikita H, Takahashi A, Endo H, et al. Preliminary study of serum tenascin-C levels as a diagnostic or prognostic biomarker of type B acute aortic dissection. *Int J Cardiol* 2013; **168:** 4267–4269.
23. Sato A, Aonuma K, Imanaka-Yoshida K, Yoshida T, Isobe M, Kawase D, et al. Serum tenascin-C might be a novel predictor of left ventricular remodeling and prognosis after acute myocardial infarction. *J Am Coll Cardiol* 2006; **47:** 2319–2325.
24. Franz M, Jung C, Lauten A, Figulla HR, Berndt A. Tenascin-C in cardiovascular remodeling: Potential impact for diagnosis, prognosis estimation and targeted therapy. *Cell Adh Migr* 2015; **9:** 90–95.
25. Golledge J, Clancy P, Maguire J, Lincz L, Koblar S. The role of tenascin C in cardiovascular disease. *Cardiovasc Res* 2011; **92:** 19–28.
26. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int* 2005; **47:** 232–234.
27. Beiser AS, Takahashi M, Baker AL, Sundel RP, Newburger JW. A predictive instrument for coronary artery aneurysms in Kawasaki

disease: US Multicenter Kawasaki Disease Study Group. *Am J Cardiol* 1998; **81:** 1116–1120.
28. Ruan Y, Ye B, Zhao X. Clinical characteristics of Kawasaki syndrome and the risk factors for coronary artery lesions in China. *Pediatr Infect Dis J* 2013; **32:** e397–e402, doi:10.1097/INF.0b013e31829dd45e.
29. Song D, Yeo Y, Ha K, Jang G, Lee J, Lee K, et al. Risk factors for Kawasaki disease-associated coronary abnormalities differ depending on age. *Eur J Pediatr* 2009; **168:** 1315–1321.
30. Ohno T, Yuge T, Kariyazono H, Igarashi H, Joh-o K, Kinugawa N, et al. Serum hepatocyte growth factor combined with vascular endothelial growth factor as a predictive indicator for the occurrence of coronary artery lesions in Kawasaki disease. *Eur J Pediatr* 2002; **161:** 105–111.
31. Terai M, Honda T, Yasukawa K, Higashi K, Hamada H, Kohno Y. Prognostic impact of vascular leakage in acute Kawasaki disease. *Circulation* 2003; **108:** 325–330.
32. Kaneko K, Yoshimura K, Ohashi A, Kimata T, Shimo T, Tsuji S. Prediction of the risk of coronary arterial lesions in Kawasaki disease by brain natriuretic peptide. *Pediatr Cardiol* 2011; **32:** 1106–1109.
33. Printz BF, Sleeper LA, Newburger JW, Minich LL, Bradley T, Cohen MS, et al. Noncoronary cardiac abnormalities are associated with coronary artery dilation and with laboratory inflammatory markers in acute Kawasaki disease. *J Am Coll Cardiol* 2011; **57:** 86–92.
34. Nakamura Y, Yashiro M, Uehara R, Watanabe M, Tajimi M, Oki I, et al. Use of laboratory data to identify risk factors of giant coronary aneurysms due to Kawasaki disease. *Pediatr Int* 2004; **46:** 33–38.
35. Koyanagi H, Yanagawa H, Nakamura Y, Yashiro M. Serum C-reactive protein levels in patients with Kawasaki disease: From the results of nation-wide surveys of Kawasaki disease in Japan. *Acta Paediatr* 1997; **86:** 613–619.
36. Ueno K, Nomura Y, Morita Y, Eguchi T, Masuda K, Kawano Y. Circulating platelet-neutrophil aggregates play a significant role in Kawasaki disease. *Circ J* 2015; **79:** 1349–1356.
37. Lin CY, Lin CC, Hwang B, Chiang BN. Cytokines predict coronary aneurysm formation in Kawasaki disease patients. *Eur J Pediatr* 1993; **152:** 309–312.
38. Shimojo N, Hashizume R, Kanayama K, Hara M, Suzuki Y, Nishioka T, et al. Tenascin-C may accelerate cardiac fibrosis by activating macrophages via the integrin alphaVbeta3/nuclear factor-kappaB/interleukin-6 axis. *Hypertension* 2015; **66:** 757–766.
39. Udalova IA, Ruhmann M, Thomson SJ, Midwood KS. Expression and immune function of tenascin-C. *Crit Rev Immunol* 2011; **31:** 115–145.
40. Karatas Z, Baysal T, Alp H, Toker A. Serum tenascin-C: A novel biomarker for diagnosis and predicting prognosis of rheumatic carditis? *J Trop Pediatr* 2013; **59:** 476–482.
41. Kotby AA, Abdel Aziz MM, El Guindy WM, Moneer AN. Can serum tenascin-C be used as a marker of inflammation in patients with dilated cardiomyopathy? *Int J Pediatr* 2013; **2013:** 608563.
42. Shukla A, Gaur P, Aggarwal A. Tenascin-C Levels, A toll-like receptor 4 ligand, in enthesitis-related arthritis category of juvenile idiopathic arthritis: A cross-sectional and longitudinal study. *J Rheumatol* 2015; **42:** 891–896.
43. Yoshikane Y, Koga M, Imanaka-Yoshida K, Cho T, Yamamoto Y, Yoshida T, et al. JNK is critical for the development of Candida albicans-induced vascular lesions in a mouse model of Kawasaki Disease. *Cardiovasc Pathol* 2015; **24:** 33–40.
44. Shimizu C, Oharaseki T, Takahashi K, Kottek A, Franco A, Burns JC. The role of TGF-beta and myofibroblasts in the arteritis of Kawasaki disease. *Hum Pathol* 2013; **44:** 189–198.
45. Kanayama M, Kurotaki D, Morimoto J, Asano T, Matsui Y, Nakayama Y, et al. Alpha9 integrin and its ligands constitute critical joint microenvironments for development of autoimmune arthritis. *J Immunol* 2009; **182:** 8015–8025.
46. Kimura T, Shiraishi K, Furusho A, Ito S, Hirakata S, Nishida N, et al. Tenascin C protects aorta from acute dissection in mice. *Sci Rep* 2014; **4:** 4051.