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Original Article

Early diagnosis of Kawasaki disease in patients with cervical lymphadenopathy

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Abstract ***Background***: Among typical patients with Kawasaki disease (KD), a few KD patients present with only fever and cervical lymphadenopathy at admission (KDL). These patients have a significant risk for misdiagnosis, delay in treatment for KD, and development of coronary artery abnormalities. Therefore, the development of an easy tool for early diagnosis in these patients is desirable.

Methods and Results: Patients who presented with only fever and cervical lymphadenopathy at admission were studied. Of these, 14 patients were eventually diagnosed with KD (KDL) and 24 patients were successfully treated using antibiotics (control). KDL patients were significantly older than control patients ($P = 0.022$). Among the laboratory findings, neutrophil counts ($P = 0.003$), C-reactive protein (CRP; $P < 0.001$), and aspartate aminotransferase (AST; $P = 0.018$) were significantly different between the groups. To discriminate KDL patients from controls, cut-off points of the aforementioned parameters (KDL indices) were determined using the receiver operating characteristic curves in order to maximize sensitivity and accuracy (age, 5.0 years; neutrophil counts, 10 000/μL; CRP, 7.0 mg/dL; AST, 30 IU/L). One point was assigned if a subject exceeded the cut-off point in a KDL index. If a patient with three or four KDL indices was considered to have KD, the sensitivity was 78% and the specificity 100%. None of the patients with one or zero KDL index developed KD.

Conclusions: KDL indices may be helpful in discriminating KDL from lymphadenitis at admission. It is important to monitor the symptoms of KD in a patient with three or four KDL indices at admission.

Key words cervical lymphadenopathy, early diagnosis, Kawasaki disease.

Kawasaki disease (KD) is a systemic vasculitis of unknown etiology that occurs commonly in children under 5 years of age and results in coronary artery abnormalities (CAA) in 15–25% of untreated children.[1–5] Its symptoms are fever, skin rash, conjunctivitis, mucosal inflammation, changes in extremities, and cervical lymphadenopathy.[1–5] Cervical lymphadenopathy is the least common diagnostic criterion and is present in approximately 42–65% of KD patients.[2,4,5] A few KD patients present with only fever and cervical lymphadenopathy at their initial presentation. These patients have a risk for misdiagnosis of bacterial lymphadenitis or other lymphadenopathy. This can sometimes lead to unnecessary treatment with antibiotics and delay in appropriate treatment including the administration of i.v. gammaglobulin (IVGG).[6–8] Delayed diagnosis and treatment with IVGG can increase the risk of the cardiac complications of KD. Zhang *et al.* examined data from a Japanese nationwide survey and reported that IVGG is more effective for patients treated at the seventh day of illness or earlier than those treated at the eighth day or later.[9] Therefore, it is important to discriminate KD patients whose initial presentation involves only fever and lymphadenopathy from those patients with other causes of cervical lymphadenopathy. Also, the development of an easy tool for early diagnosis in these patients is desirable. With this in mind, we retrospectively reviewed the data of patients who were referred and admitted with symptoms of fever and cervical lymphadenopathy on initial presentation.

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Methods

Patients

Of the 154 patients who were referred and admitted to the Kagoshima City Medical Association Hospital (KCMA Hospital) between September 1998 and August 2004 and ultimately fulfilled the diagnostic criteria of the Japanese Kawasaki Disease Research Committee[2] during the course of the disease, those patients who had only fever and cervical lymphadenopathy at admission were used as KDL patients. Patients who were referred and admitted to KCMA Hospital and were diagnosed

with lymphadenitis during the same period were used as control patients. Patients with infectious mononucleosis (IM) were excluded.

Between KDL patients and control patients, their information (age, sex, and admission day of illness) and laboratory findings at the time of admission (white blood cell counts, neutrophil counts, hematocrit, platelet counts, C-reactive protein [CRP]; aspartate aminotransferase [AST]; alanine aminotransferase; lactate dehydrogenase; total protein; and albumin) were compared. Ultrasound echocardiography was performed in patients with KD and control at admission and re-performed at least twice a week during admission. The findings and maximum diameters of lymph nodes in each patient or control evaluated on ultrasonography were also compared. Ultrasonographic evaluations of cervical lymph nodes using a 7.5MHz transducer of a B-mode sector scanner (Logiq 500 Pro, GE Medical System, Tokyo, Japan) were performed on admission. The maximum lymph node diameter was measured using ultrasonography and defined as the maximum diameter of the largest cervical mass constituted by multiple lymph nodes.

Illness day 1 was determined as the first day of fever in both groups. Informed consent was obtained from each child's parents before routine blood sampling and ultrasonography.

Statistical analysis

Differences in mean values of age, admission day, laboratory findings, and the maximum diameter of lymph node between KD and control patients were examined using Mann–Whitney *U*-test. Differences between KD and IM patients were also examined using Mann–Whitney *U*-test. Fisher's exact probability test was used to assess the frequency of male subjects and the type of lymphadenopathy between the groups. Cut-off point analysis using receiver operating characteristic (ROC) curves was applied to maximize the sensitivity and accuracy for discriminating KDL patients from controls. The data were processed using Stat View 5.0 (Abacus Concepts, Berkeley, CA, USA) and SPSS 14.0 (SPSS, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Characteristics of subjects

During the study period, 14 patients (9.1% of total patients with KD) had only fever and cervical lymphadenopathy at admission. All of them eventually fulfilled the diagnostic criteria between the fourth day and eighth day of illness (5.0 ± 1.1 days of illness). Thirteen patients received IVGG (2.0 ± 0.6 g/kg) and four patients needed additional IVGG. One patient had desquamation on his hands on the eighth day of illness and was then diagnosed with KD. Because he had already become afebrile, he was not given IVGG, and fortunately CAA was not observed. Two patients developed CAA as estimated on ultrasound echocardiography at 1 month of illness. Both patients were admitted at 2 days of illness and were started IVGG on 6 days of illness.

Twenty-four patients (16 boys, eight girls; average age, 4.8 ± 4.5 years, range 0.1–15.4 years) were referred and admitted with only fever and lymphadenopathy (control). They became afebrile following antibiotic therapy (2.8 ± 1.8 days from the initiation of i.v. antibiotics). There were no patients who required aspiration of an abscess. All of them were diagnosed with lymphadenitis or suspected lymphadenitis related to drainage area. None of them had coronary artery changes in ultrasound echocardiography performed during admission. Desquamation of the fingers or toes after discharge was not observed in the controls.

Comparisons of the findings between KDL and control patients are shown in Table 1. There were no differences in the incidence of male gender between patients with KDL and control patients. The mean age was significantly higher in KDL patients than in control patients. The mean admission day of illness was significantly earlier in KDL than in controls. Among 11 patients admitted at 5 days of illness or later, no patients developed KD.

Laboratory and lymph node findings

For the laboratory findings at the time of admission, KDL patients had significantly higher white blood cell counts, neutrophil

Table 1 Clinical findings

	KDL	Control	IM	*P**
n (M/F)	14 (10/4)	24 (16/8)	36 (20/16)	n.s.
Age (years)	6.6 ± 2.3	4.8 ± 4.5	5.5 ± 3.5	0.022
Admission day	2.9 ± 0.9	5.1 ± 3.2	6.0 ± 3.0	0.003
WBC (mm^3)	18 043 ± 6380	12 729 ± 7,209	14 267 ± 4560	0.043
Neutrophil counts (/μL)	14 433 ± 5594	8128 ± 5170	3799 ± 1715	0.003
Hematocrit (%)	36.9 ± 2.8	35.5 ± 3.5	36.7 ± 5.5	n.s.
Platelet counts(× 10^4/μL)	30.2 ± 11.3	31.7 ± 13.1	19.9 ± 6.2	n.s.
CRP (mg/dL)	10.6 ± 4.9	5.2 ± 3.4	1.3 ± 1.0	<0.001
AST (IU/L)	143 ± 207	31 ± 13	117 ± 129	0.018
ALT (IU/L)	106 ± 150	23 ± 17	144 ± 209	n.s.
LD (IU/L)	685 ± 332	637 ± 360	1049 ± 317	n.s.
Albumin (g/dL)	4.0 ± 0.4	4.0 ± 0.3	3.9 ± 0.3	n.s.
Lymph node maximum diameter (mm)	19.4 ± 6.7 (n = 5)	21.5 ± 6.1 (n = 15)		n.s.

P were measured between KDL and control. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IM, infectious mononucleosis; KDL, patients with Kawasaki disease who had only fever and lymphadenopathy at admission; LD, lactate dehydrogenase; admission day; admission day of illness; WBC, white blood cells.

counts, CRP, and AST than those of control patients (Table 1). Lymphadenopathy was noted at 1.5 ± 0.6 days of illness in KDL patients versus at 2.3 ± 1.6 days in control patients. These illness days were not statistically different between the groups ($P = 0.227$).

Four KDL patients (29%) and 10 control patients (42%) demonstrated bilateral cervical lymphadenopathies. This difference was not statistically significant. Ultrasonography was performed in five patients with KDL and in 15 control patients. Multiple enlarged lymph nodes were observed in five KDL patients (Fig. 1a) and 14 control patients (Fig. 1b). Only one control patient had a large central hypoechoic component with small nodes. Maximum lymph node diameter was not different between the groups (Table 1).

Discriminating KDL patients from control patients

In order to discriminate KDL patients from control patients, the four KDL indices (age, neutrophil counts, CRP, and AST) were selected according to the level of their significance (area under the ROC curves of these indices were 73%, 80%, 83%, and 73%, respectively). White blood cell counts had a strong relationship with neutrophil counts ($r = 0.934$, $P < 0.001$), therefore we represented this by neutrophil counts. Admission illness day was also significantly different between the groups but we did not use it because the indication for referral of admission may be different for each physician. The following optimal cut-off points were used to discriminate KDL patients from controls: age 5.0 years (sensitivity 71%, specificity 67%); neutrophil count 10000/μL (sensitivity 86%, specificity 67%), CRP 7.0 mg/dL (sensitivity 93%, specificity 67%), and AST 30 IU/L (sensitivity 71%, specificity 67%). One point was assigned if a subject's value exceeded the cut-off in a KDL index. The mean number of abnormal KDL indices was 3.2 ± 0.8 (range, 2–4) in KDL patients and 1.3 ± 0.7 (range, 0–2) in control patients (Fig. 2). These were significantly different ($P < 0.0001$). If a patient with three or four abnormal KDL indices is considered to have KD, the sensitivity was 78% (11 of 14) and specificity was 100% (24 of 24). Of 11 patients with three or four abnormal KDL indices, seven patients had five or six principal symptoms of KD on the fifth day of illness. Two patients had four symptoms and each one patient had three or two symptoms. Therefore, KDL indices were helpful in discriminating patients with KD from patients with lymphadenitis, even in four patients who were diagnosed as having KD after the fifth day of illness. If a patient with two or more abnormal KDL indices is considered to have KD, the sensitivity was 100% (14 of 14) and specificity was 50% (12 of 24). None of the patients with one or zero KDL indices developed KD. The number of KDL indices in the control patients decreased gradually after the initiation of antibiotics. There were no control patients who had increases in number of KDL indices during the clinical course.

Patients with IM

Thirty-six patients were also referred and admitted with only fever and lymphadenopathy during the study period but they were excluded from designation as control patients because they had atypical lymphocytes ($36 \pm 13\%$ of total white blood cells, range 11–65%) in the peripheral blood at admission. Of these, 27 were ultimately diagnosed on later serum antibody studies with IM caused by the Epstein–Barr virus. The remaining nine patients were diagnosed with IM according to clinical course. None of them developed CAA.

Patients with IM had significantly lower white blood cell counts ($P < 0.0001$), neutrophil counts ($P < 0.0001$), platelet counts ($P = 0.0006$), and CRP ($P < 0.0001$) than those of patients with KD (Table 1). Lactate dehydrogenase in IM patients was significantly higher than that of KDL patients ($P = 0.0003$). The mean number of abnormal KDL indices in IM patients was 1.5 ± 0.7 (range, 0–2), and it was significantly lower than that in KDL patients ($P < 0.0001$). There were no IM patients who had three or four abnormal KDL indices.

Discussion

There are many conditions that can cause lymphadenopathy, such as KD, malignancies, mononucleosis, streptococcal/staphylococcal adenitis or tonsillitis, and toxoplasmosis.[10] Patients with IM also have fever and lymphadenopathy, but in the present

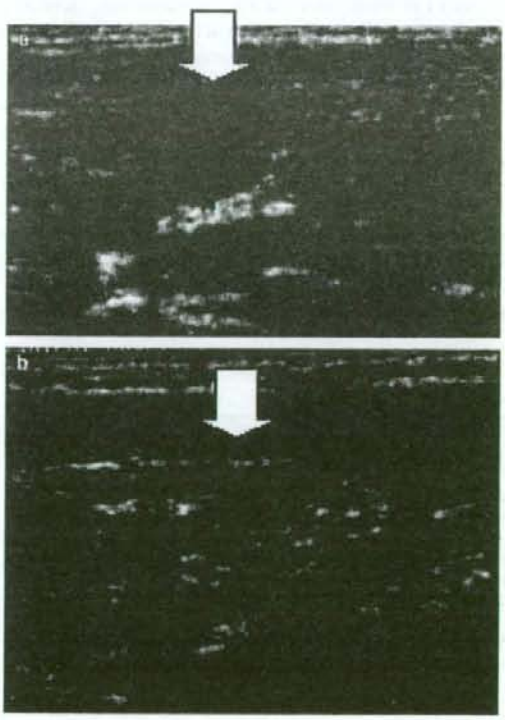

Fig. 1 Ultrasonography of cervical lymph nodes. (a) Patients with Kawasaki disease had multiple enlarged lymph nodes (arrow). (b) Fourteen patients with lymphadenitis also had multiple enlarged lymph nodes (arrow).

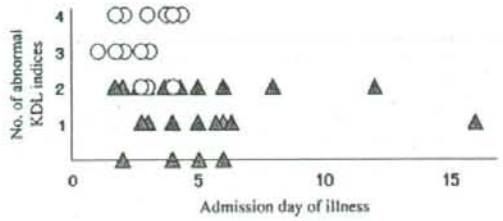

Fig. 2 Distribution of the number of KDL indices in patients with Kawasaki disease (KD) and lymphadenitis. (○) Patients with KD had 2–4 abnormal KDL indices, and (▲) patients with lymphadenitis had 0–2 abnormal KDL indices. The admission days of illness were earlier in patients with KD than in patients with lymphadenitis. KDL, patients with Kawasaki disease who had only fever and lymphadenopathy at admission; abnormal KDL indices: age ≥ 5.0 years; neutrophil counts ≥ 10 000/μL; C-reactive protein ≥7.0 mg/dL; alanine aminotransferase ≥30 IU/L.

study it was not difficult to exclude these patients from the control or KDL patients using peripheral blood differential findings.

Commonly, KD patients had several clinical features of KD at admission. Among typical KD patients, a few patients present with only fever and cervical lymphadenopathy on admission (9.1% at KCMA Hospital). These patients have a significant risk for misdiagnosis, unnecessary treatment with antibiotics, delay in treatment for KD, and development of CAA.[6–8] Kao *et al.* reported on 14 patients with KD who presented with cervical lymphadenitis or deep neck infection.[8] All of them were treated with antibiotics and eventually fulfilled the diagnostic criteria for KD at an average of 8.2 days of illness (6–20 days). CAA were observed in three patients (21%). They concluded that KD should be considered in a child who has a fever and an enlarged cervical lymph node and who is unresponsive to empiric antibiotics. After confirming unresponsiveness to antibiotics, it may take several days before diagnostic criteria for KD are met, as seen in the Kao *et al.* report. This delay subsequently results in a delay in treatment for KD. Based on clinical experience with many KD patients, any symptoms of KD are monitored at KCMA Hospital, such that the diagnosis of KDL was established at 2.1 days after admission, and IVGG therapy was initiated (average on the fifth illness day). This situation might not be possible in all hospitals. Therefore, an easy tool for early diagnosis for KDL patients is desirable.

Tashiro *et al.* reported that ultrasonographic evaluation was useful in the diagnostic process among KD patients with a cervical mass and presumed bacterial lymphadenitis at an early stage of the disease.[11] They reported that multiple hypoechoic-enlarged nodes forming is a feature of KD, whereas a large central hypoechoic component with small nodes is a feature of the presumed lymphadenitis. In the present study, however, ultrasonography of lymphadenitis patients (control patients) showed multiple hypoechoic-enlarged nodes forming (Fig. 1b). In Tashiro *et al.*'s report the cervical masses of lymphadenitis were larger(46 ± 18 mm in diameter) than those in the present study. Therefore, the severities in lymphadenitis of the control patients of the present study were different from those in presumed bacterial lymphadenitis patients in Tashiro's report. This difference may cause the difference in ultrasonographic findings in the lymph nodes.

To discriminate KDL from controls, we chose four KD indices: age, neutrophil count, CRP, and AST. Lymphadenopathy is observed more frequently in older patients with KD than in infants with KD.[6,12] The average age of 6.6 years was markedly higher than that of usual patients with KD (mean KD patient age at KCMA Hospital during the study period was 2.5 ± 2.2 years). Because of this, KD patients were significantly older than control patients. With regard to neutrophil counts and CRP, their significance may be caused by the difference in inflammation. Because KD is a disease of systemic vasculitis,[3,5] it is not surprising that inflammation in KDL patients was greater than in control patients who had more localized inflammation. Liver dysfunction is well known in KD[1–5] and is the reason for the significant difference in AST between KDL and control patients. These four indices were considered as part of the characteristics of patients with KD, and we were thus able to identify 78% of KDL patients at admission using these indices. Among the patients who had only fever and lymphadenopathy on admission, it was important to monitor other symptoms of KD when three or four KDL indices were abnormal. In contrast, none of the patients with zero or one abnormal KDL indices developed KD.

Conclusions

There were many patients who presented with only fever and lymphadenopathy on admission. The KDL indices, which are constructed from the data of age and routine blood examination, are helpful in discriminating patients with KD from patients with lymphadenitis at admission.

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臨床研究・症例報告

免疫グロブリン大量療法後に著しい血小板減少を来した川崎病の1例

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要　旨

生来健康の3歳男児。3病日に頸部リンパ節炎の診断で入院した時の血小板数は23.2万/μℓであった。6病日までに6主要症状を認め川崎病と診断したが，血小板数は13.7万/μℓまで低下していた。免疫グロブリン大量療法（IVIG，1g/kg）を2日間施行したが解熱せず，血小板数の著減（8病日：0.6万/μℓ）を来した。骨髄は血小板放出像がほとんどみられない幼弱な巨核球の増加がみられ，PAIgG は 467ng/10^7cells だった。製剤を変更した IVIG 追加でも解熱せず，12病日からのステロイドパルス療法で解熱した。血小板数は製剤を変更した IVIG 後の12病日には7.0万/μℓまで上昇し，その後正常化した。IVIG は川崎病や特発性血小板減少性紫斑病（ITP：idiopathic thrombocytopenic purpura）の主な治療であるが，IVIG 後に血小板数が減少した ITP 例の報告もあり，IVIG 後に稀に著明な血小板減少を来す場合があるという認識は必要と思われた。

[小児科臨床　61：985，2008]

KEY WORDS　Kawasaki Syndrome, intravenous immunoglobulin, idiopathic thrombocytopenic purpura

はじめに

特発性血小板減少性紫斑病（ITP：idiopathic thrombocytopenic purpura）は血小板膜蛋白に対する自己抗体の発現により，主に脾における血小板の破壊が亢進し血小板減少を来す自己免疫性疾患である。病因としてウイルス感染など先行感染の関与が推測されているが抗体産生の機序は明らかではない[1]。川崎病は5歳以下の小児における中動脈を主体とした病因不明の血管炎症候群である[2]。川崎病に合併した ITP は極めて稀であり，また近年の報告がないため急性期に合併し免疫グロブリン大量療法（IVIG：intravenous immunoglobulin）が行われた報告はない。

我々は川崎病に対する IVIG 後に著明な血小板減少を来した1例を経験した。IVIG は川崎病においても ITP においても最もよく行われる治療であり，本例の経過は興味深いものと考えられ報

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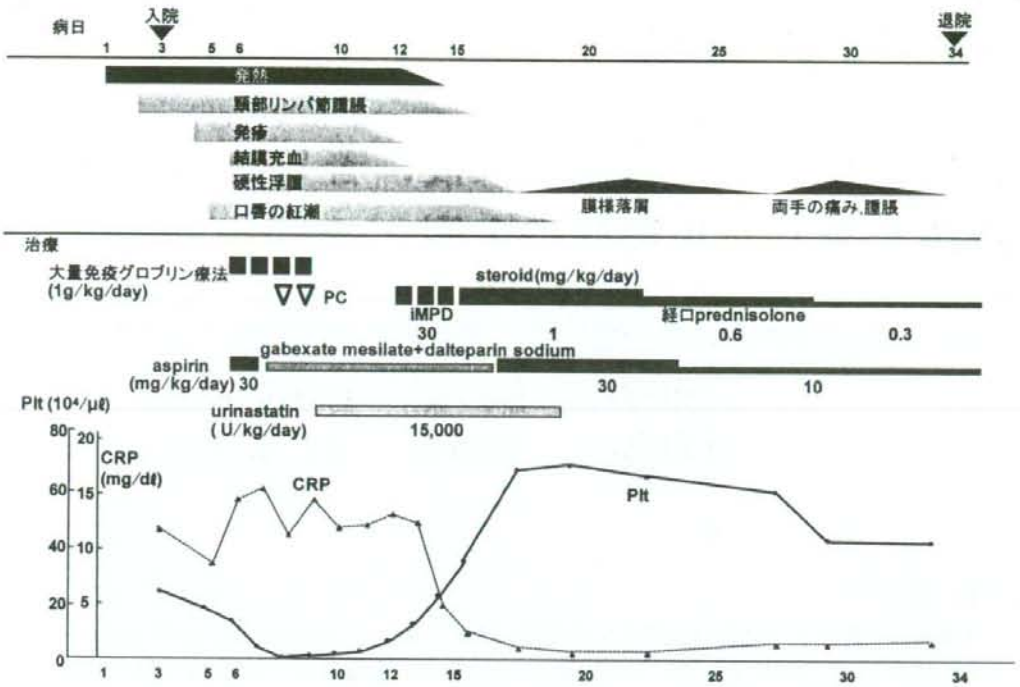

図 臨床経過

Plt : platelet count, CRP : C-reactive protein, PC : platelet concentrates, iMPD : intravenous methylprednisolone.

告する。

症 例

5歳6カ月の男児で同胞は妹が1人。血液疾患などの家族歴はなかった。在胎40週，正常分娩で出生体重は2,830gであり，発育・発達は正常だった。

入院2週間前より鼻汁を認めていた。発熱，咽頭痛があり近医小児科を受診し，抗菌剤の投与が行われた。高熱が続き左頸部リンパ節腫脹も出現したため，3病日に同院を再診し，頸部リンパ節炎の診断で当科紹介入院した。

入院時は身長107cm（+0.2 SD），体重16.5kg（+0.2 SD），体温40.2°Cだった。眼球・眼瞼結膜には貧血・黄染・充血を認めず，左頸部には2 cm×3 cm大で弾性硬の腫瘤を触知した。咽頭発赤を認めたが，口唇の紅潮・苺舌はみられなかった。心拍数は142回/分で心雑音や過剰心音はなかった。発疹や肝脾腫もなく，四肢の出血斑や浮腫もなかった。

化膿性頸部リンパ節炎の診断で，抗菌剤の静脈投与を開始したが解熱せず，4病日に体幹を中心に発疹が出現し，5病日に口唇の紅潮もみられるようになった。6病日に眼球結膜充血と四肢の硬性浮腫が出現し，川崎病と診断した（原田のスコア6/7点）。入院時の白血球数は16,600/μℓ，CRP値は11.9mg/dℓであったが，川崎病診断時（6病日）には白血球数は6,700/μℓ，CRP値は14.5mg/dℓとCRP値の上昇を認めた。また，血小板数は23.2万/μℓから13.7万/μℓまで低下していた。同日よりaspirin 30mg/kg/dayの内服とIVIG（1g/kg×2回）を施行したが解熱しなかった。血小板数はIVIG翌日（7病日）には4.7万/μℓまで低下しaspirinの内服を中止した。翌8病日には血小板数が0.6万/μℓまで低下し，四肢と顔面に出血斑や点状出血が出現した。凝固系の検査では，PT-INR 1.16，APTT 45.5秒，fibrinogen 578mg/dℓ，D-ダイマー14.9 μg/mℓで，播種性血管内凝固症候群（DIC：disseminated intravascular coagulation）の旧厚生省診断基準

表　急性期に ITP を合併した川崎病の報告

報告者（引用文献）	年齢/性	最低血小板数（病日）	川崎病の治療	ITP の治療	血小板数の経過
Hara et al (4)	2 y/M	$6.0\times10^4/\mu\ell$（6病日）	記載なし	無治療	正常範囲に回復
清水ら (6)	7 m/M	$2.3\times10^4/\mu\ell$（9病日）	aspirin	経口 prednisolone	退院4カ月後に脳内出血で死亡
梅里ら (7)	1 y/F	$2.1\times10^4/\mu\ell$（17病日）	aspirin	経口 prednisolone	正常範囲に回復
石黒ら (8)	1 y/F	$3.0\times10^4/\mu\ell$（9病日）	aspirin	IVIG	正常範囲に回復
本症例	5 y/M	$0.6\times10^4/\mu\ell$（8病日）	IVIG steroid pulse	IVIG（別製剤） steroid pulse	正常範囲に回復

スコアは5点と診断基準をみたさなかった。骨髄所見では血球貪食像はなく，血小板放出像がほとんどみられない幼弱な巨核球が多数を占めており，ITP の骨髄像に矛盾しなかった。別製剤による IVIG（1 g/kg×2回）を8病日から追加し，8病日・9病日に血小板輸血を施行，gabexate mesilate, dalteparin sodium も持続投与を開始した。12病日に血小板数は7.0万/$\mu\ell$まで上昇したが，発熱は持続しステロイドパルス療法（methylprednisolone 30mg/kg/day）3日間を行い解熱した。後療法として経口 prednisolone（1 mg/kg/day）を開始し21日間で漸減中止した。漸減中に発熱はないものの両手の腫脹，疼痛を訴え，CRP 値も一過性の上昇が軽度みられた。血小板数の減少は川崎病の回復期にはみられず，33病日は41.2万/$\mu\ell$であった。冠動脈後遺症なく34病日に退院した。後日判明した8病日の PAIgG は467ng/10^7cells（正常値9～25）と上昇していたが，抗血小板抗体は陰性であった。また，本例で使用したのと同一製剤で免疫グロブリン製剤のリンパ球幼若化試験（DLST）を施行したが陰性であり，製剤内の抗血小板抗体も陰性であった。

考　案

川崎病では，急性期の血小板数の低下は重症度の指標とされ，原田のスコアの項目の一つとしても採用されている[3]。Hara らは，486人の川崎病のうち10人（2.0%）に15万/$\mu\ell$以下の重度の血小板減少がみられ，その10人の血小板数の最低値は9.4±3.8万/$\mu\ell$（6.8±2.2病日）だったと報告している[4]。川崎病における血小板数の低下の原因として，川崎病自体の血管炎による血小板の消費（DIC），aspirin 投与の影響，血球貪食症候群の合併，ITP の合併，免疫グロブリン製剤の副反応などが考えられる[5]。本例は，DIC スコアは5点であり，aspirin 投与中止後も血小板減少が続き，骨髄像で貪食像がみられなかった。また，IVIG 前より血小板数が13.7万/$\mu\ell$と低下傾向を認めており，これは，川崎病自体の血管炎，もしくは ITP の合併によるものを考えた。PAIgG 値は上昇していたが IVIG 後であることと，PAIgG の検査自体が ITP の診断としての特異度が低く，血小板膜糖蛋白 GPIIb-IIIa もしくは GP I b-IX に対する特異抗体などのさらなる検索が必要と考えられた。

急性期に ITP を合併した川崎病の症例報告は調べ得た範囲内では4例[4)6)~8)]（表）だった。いずれも1980年代の報告であるため川崎病に対する IVIG の確立前であり，全例が aspirin のみで治療されている。合併した ITP に対しては経口 prednisolone や川崎病軽快後に IVIG 治療が行われ，1例を除いては血小板数が回復している。本

例では，ITP の主な治療でもある IVIG を施行したが，その直後に血小板数の著減がみられた点が特に興味深い。

ITP に対する IVIG の血小板増加機序については，種々の可能性が考えられているが，投与された大量の免疫グロブリンによってマクロファージや樹状細胞の Fcγ レセプターをブロックすることにより，マクロファージが IgG 結合血小板を補足することを阻害することが主な作用機序と考えられている[9]。しかし，IVIG により極めて稀に血小板数の低下がみられることも知られている。ITP 合併妊婦に IVIG を行った後に，血小板減少が進行した 2 例の報告があり[10][11]，そのうちの 1 例では免疫グロブリン製剤に含まれている human platelet antigens に対する抗体が血小板減少の原因である可能性を述べている[11]。しかし，本例では血小板抗体は陰性だった。

IVIG の追加の際には別の製剤に変更を行った。IVIG 追加後，川崎病に対しての効果は不十分であったが，血小板数の上昇がみられ，製剤変更 5 日後（12病日）には7.0万/μℓ と増加していた。製剤はいずれも，ポリエチレングリコール処理であり，1 回目・2 回目の製剤の human platelet antigen に対する抗体の差も含め違いはなかったが，変更後には血小板数の上昇が得られた。この上昇は IVIG の効果が考えやすいが，自然軽快も必ずしも否定はできない。

ITP で血小板数減少の報告がみられた例が 2 例とも妊婦であり，今回は川崎病に合併したものであった。妊娠中には種々の免疫学的な異常を来し[12]，川崎病においても免疫の異常活性化を来している[13]。何らかの免疫異常が血小板減少に関与したことも考えられる。これまでに本例のような報告はなかったが，稀にみられる合併症としての認識は重要と考えられた。

結　語

川崎病急性期に血小板減少がある場合には，IVIG 後に稀に著明な血小板減少を来す可能性がある。

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Marked thrombocytopenia after high dosage of intravenous immunoglobulin in a patient with Kawasaki Syndrome

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We reported a case of 3-year-old boy with Kawasaki syndrome (KS) who developed marked thrombocytopenia after high dosage of intravenous immunoglobulin (IVIG). He had an unremarkable medical past history and was referred to our hospital because of lymphadenitis with the 3days of fever. The platelet count was $23.2\times10^4/\mu\ell$ on admission. When he was diagnosed with KS at the 6th day of illness, his platelet count had decreased to $13.7\times10^4/\mu\ell$. Treatments with oral administration of aspirin (30mg/kg/day) and IVIG (1g/kg×2days) were initiated. Despite the treatment, his fever continued and his platelet count decreased to $0.6\times10^4/\mu\ell$. Bone marrow findings revealed increase of immature meagakaryocytes without releasing of platelet and PAIgG was high titer of 467 ng/10^7 cells, suggesting idiopathic thrombocytopenic purpura (ITP). After an additional IVIG (1g/kg×2days) treatment using another pharmaceutical, platelet count increased to $7.0\times10^4/\mu\ell$ at the 12th day of illness and then elevated to normal range. However, his fever continued, then, intravenous steroid pulse therapy was initiated at the 12th day of illness, and his fever quickly disappeared. Thrombocytopenia after IVIG has been reported in patients with ITP. IVIG is commonly used for KS or ITP. It is necessary to know the fact marked thrombocytopenia could occur after IVIG.

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Patient Reports

Selective IgA deficiency complicated by Kawasaki syndrome

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Key words immunoglobulin therapy, Kawasaki syndrome, selective IgA deficiency, steroid.

Selective absence of serum IgA is the most common defect among primary immunodeficiency diseases, with rates ranging from 1/333 to 1/16 000 persons among different races.[1] Serum antibodies to IgA are reported in as many as 44% of patients with selective IgA deficiency.[1] In these patients, administration of blood products containing IgA may cause severe or fatal anaphylactic reactions. Therefore, administration of blood products is usually considered a contraindication for patients with selective IgA deficiency.

A 2-year-old boy with selective IgA deficiency complicated by Kawasaki syndrome (KS) was admitted to Izumi City Hospital. For patients with KS, administration of a high dosage of i.v. immunoglobulin (IVIG) and the oral administration of aspirin are recommended.[2,3] The present patient, however, needed treating without the use of IVIG. We successfully treated him using i.v. administration of methylprednisolone instead of IVIG. This is the first report of selective IgA deficiency complicated by KS.

Case report

The patient was born to healthy parents after an uncomplicated pregnancy by spontaneous vaginal delivery after 38 weeks and weighed 2865 g. There was no family history of a tendency for any infections. His development was normal, as had been that of his elder sister. No specific episodes were observed during the course of chickenpox or after vaccinations (bacille Calmette–Guérin, diphtheria–pertussis–tetanus, polio, measles, and rubella).

When the boy was 2 years old he was referred and admitted to Izumi City Hospital because of a 5 day persistent high fever, conjunctival injection, red cracked lips and tongue, diffuse erythematous macular rash, swelling of bilateral hands, and anorexia.

On physical examination his height was 90 cm (+0.2 SD), weight 13.0 kg (+0.2 SD), and body temperature was 39.4°C. He appeared remarkably ill. Tachycardia was observed but heart murmur, gallop rhythm, and hepatosplenomegaly were not observed.

Initial laboratory findings (Table 1) indicated severe inflammation (white blood cell [WBC] count, 11 800/μL; C-reactive protein [CRP], 8.6 mg/dL; erythrocyte sedimentation rate 100 mm/h), hyponatremia and hyperbilirubinemia. A normal level of IgG and extremely low level of IgA (2 mg/dL) were observed. Echocardiography indicated normal left ventricular wall motion and normal coronary arteries.

With a diagnosis of KS (Harada's score 4/7) and selective IgA deficiency, treatments with oral administration of aspirin (30 mg/kg per day) and urinastatin (15 000 U/kg per day) instead of IVIG were initiated (Fig. 1). Despite treatment with an increased dosage of aspirin of up to 50 mg/kg per day and urinastatin up to 25 000 U/kg per day, his symptoms did not improve and laboratory findings worsened (WBC 14 800/μL; CRP 18.1 mg/dL). I.v. steroid pulse therapy (methylprednisolone 30 mg/kg per day for 3 days) was initiated on the eighth day of illness. His fever disappeared after the first administration of methylprednisolone, while other symptoms and laboratory findings improved gradually. Oral administration of prednisolone (1 mg/kg per day) was started after the i.v. therapy, and the dosage of prednisolone was gradually reduced. After stopping the administration of prednisolone on the 20th illness day, he complained of mild pain and swelling of both hands; a slight increase in CRP was also observed. Because he had no fever, no additional therapy was attempted and his symptoms and laboratory findings eventually improved. He was discharged without coronary artery abnormalities on the 26th illness day.

Later examinations indicated that his parents had normal levels of IgA, but that his sister had a low level. The patient was also confirmed to have a high level of an anti-IgA antibody (Fig. 2).

Discussion

Roweley *et al.* investigated the role of IgA immune response in patients with KS and proposed a respiratory portal of entry for the agent, which then elicits an oligoclonal IgA response.[2] The present patient, who had IgA deficiency, developed KS; this cannot be explained using the Rowley *et al.* hypothesis, hence this is an interesting fact considering the mechanism of development of KS.

In some families, selective IgA deficiency exhibits autosomal recessive inheritance.[1] Clinical symptoms of the disease vary from opportunistic infection to asymptomatic varieties.[1] Among some apparently healthy blood donors, 0.33% are reported to have selective IgA deficiency.[1] To diagnose patients with selective IgA deficiency, it is necessary to confirm the

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Table 1 Laboratory findings at admission

Peripheral blood analysis
WBC 11 800 μL (neutrophil 82%, lymphocyte 14%, monocyte 3%)
RBC 375 × 10^4 μL
Hemoglobin 10.5 g/dL
Hematocrit 29.7%
Platelets 29.1 × 10^4 μL
Chemical analysis
AST 48 IU/L
ALT 91 IU/L
Lactate dehydrogenase 293 IU/L
Total protein 6.1 g/dL
Albumin 3.9 g/dL
Total bilirubin 2.8 mg/dL
Direct bilirubin 2.1 mg/dL
Glucose 91 mg/dL
Blood urea nitrogen 10 mg/dL
Creatine 0.35 mg/dL
Na 129 mEq/L
K 4.5 mEq/L
Cl 91 mEq/L
Immunological analysis
C-reactive protein 8.6 mg/dL
Erythrocyte sedimentation rate 100 mm/h
IgG 584 mg/dL
IgA 2 mg/dL
IgM 104 mg/dL

ALT, alanine aminotransferase; AST, aspartate aminotransferase; RBC, red blood cells; WBC, white blood cells.

serum level of IgA (<10 mg/dL).[1] In infants or young children, diagnosing them with selective IgA deficiency is not easy because transient low levels of IgA are sometimes observed; therefore, re-examination after an adequate interval is necessary in such situations.[1] The present patient had persistent low levels of IgA; additionally, his elder sister also had a low level of IgA, whereas that of the parents was normal. These data suggest autosomal recessive inheritance in this family. IgA deficiency shares some clinical, laboratory, and genetic features with common variable immunodeficiency. Rachid *et al.* reported that patients with common variable immunodeficiency and IgA

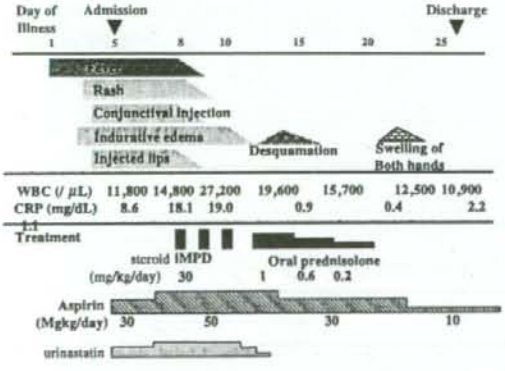

Fig. 1 Clinical course. CRP, C-reactive protein; iMPD, i.v. methylprednisolone; WBC, white blood cells.

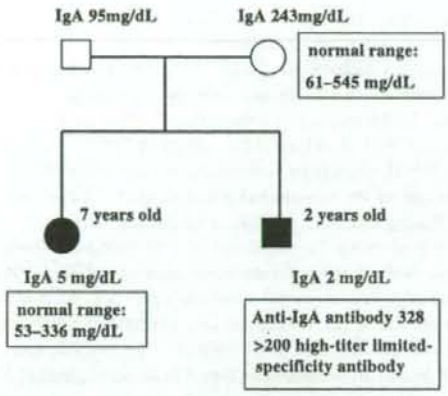

Fig. 2 Immunological findings of the patient's family. Additional immunological study of the patient: IgG, 553 mg/dL; IgG_1, 513 mg/dL; IgG_2, 32.3 mg/dL; IgG_3, 7.4 mg/dL; IgG_4, <3.0 mg/dL; IgM, 104 mg/dL; C3, 96 mg/dL; C4, 18 mg/dL; anti-nuclear antibody (–).

deficiency have mutations of *tumor necrosis factor receptor superfamily, member 13B* (*TNFRSF13B*), which encodes for the transmembrane activator and the calcium-modulator and cyclophilin-ligand interactor, a member of the tumor necrosis factor-receptor superfamily.[4] Unfortunately, gene analysis was not carried out in the present patient because parental informed consent was not obtained.

Recurrent sinopulmonary infections are the most frequent illness associated with selective IgA deficiency, and 7–36% of patients have complications due to autoimmune diseases such as systemic lupus erythematosus, Sjögren's syndrome or juvenile idiopathic arthritis.[5,6] Some patients with epilepsy or mental retardation may have complications due to selective IgA deficiency, and some have a secondary IgA deficiency due to the administration of anti-epileptic drugs.[7,8] To screen for IgA deficiency, interviewing patients on medical history or family history may be informative, but in patients such as the present one it is not possible to diagnose IgA deficiency without measuring the level of IgA in serum. An important problem thus arises in the treatment of patients with KS because IVIG is the most important treatment for KS.

Shock is a well-known adverse effect in treatments involving immunoglobulin preparations; 17 of 4719 patients (0.36%) had shock linked to IVIG.[9] Some with selective IgA deficiency may be included among these patients. To avoid shock from IVIG treatment, it is necessary to determine the IgA level at admission for patients with KS. At Izumi City Hospital as well as hospitals related to Kagoshima University, the measurement of immunoglobulins (IgG, M, and A) is one of the recommended routine examinations for patients with KS at admission. It is not always possible, however, to estimate the IgA level in KS patients prior to administration of IVIG. Routinely measurement of immunoglobulin prior to IVGG is preferable, but when this is not possible, providing sufficient screening for selective IgA deficiency by interviewing would be important. When selective IgA deficiency

is suspected, IVIG treatment should be postponed until the immunoglobulin level is confirmed.

Most KS patients are treated using IVIG, although known alternative treatments include oral or i.v. steroids, neutrophil elastase inhibitors, or plasmapheresis.[2,3,10] Commonly, such treatments are used as additional therapies with IVIG or in refractory cases.[2,3,10] Although steroid treatment in patients with IVIG-resistant KS is one of the recommended treatments,[2,3,10] initial treatment of KS using steroids has not been established. There are reports, however, showing the usefulness of such treatments (combined with or without IVIG) for an initial treatment of KS.[9] Although further study is necessary to clarify the effect of steroids as an initial treatment of KS, the present case illustrates the usefulness of i.v. methylprednisolone in the initial treatment of KS, and that it might also be an alternative treatment in the acute phase of KS.

Conclusions

Because IVIG is contraindicated in patients with selective IgA deficiency, in a patient suspected to have selective IgA deficiency, IVIG should be postponed until the immunoglobulin level is confirmed. In a patient with selective IgA deficiency, treatment with i.v. methylprednisolone may be a useful therapeutic alternative to IVIG.

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ORIGINAL PAPER

Effects of methylprednisolone pulse on cytokine levels in Kawasaki disease patients unresponsive to intravenous immunoglobulin

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Abstract This study aimed to determine the effects of intravenous methylprednisolone pulse (IVMP) therapy on cytokine levels in patients with acute Kawasaki disease (KD) unresponsive to initial intravenous immunoglobulin (IVIG) therapy. Fifteen KD patients unresponsive to initial IVIG, 2 g/kg/day, were randomized to receive IVMP (n=7), 30 mg/kg/day for 3 days or additional IVIG (n=8), 2 g/kg/day, and plasma cytokine levels were compared. The fraction of febrile patients was significantly lower in the IVMP group than in the additional IVIG group on day 2 (0/7 vs. 3/8, p=0.03), but not on day 4 and later (3/7 vs. 4/8, p=1.00) because of recurrent fever. The prevalence of coronary lesions was similar between the two groups (2/7 vs. 2/8, p=1.00). The ratios of plasma levels of tumor necrosis factor-α and monocyte chemoattractant protein-1 to those at enrollment (defined as day 1) were significantly lower in the IVMP group on day 4 (0.50±0.27 vs. 1.01±0.46, 0.53±0.39 vs. 0.93±0.44, p=0.02 and 0.045, respectively), but not on day 7 (0.54±0.34 vs. 0.88±0.39, 0.76±0.39 vs. 0.61±0.17, p=0.07 and 0.83, respectively). The ratios of interleukin-2 receptor, interleukin-6, and vascular endothelial cell growth factor to those at enrollment did not differ significantly between the two groups. In conclusion, for KD patients unresponsive to initial IVIG, IVMP suppresses cytokine levels faster, but subsequently similarly, compared with additional IVIG.

Keywords Cytokine · Kawasaki disease · Steroid pulse

Abbreviations

IVIG	Intravenous immunoglobulin
IVMP	Intravenous methylprednisolone pulse
IL-6	Interleukin-6
KD	Kawasaki disease
MCP-1	Monocyte chemoattractant protein-1
sIL-2R	Soluble interleukin-2 receptor
TNF-α	Tumor necrosis factor-α
VEGF	Vascular endothelial cell growth factor

Introduction

An optimal management of patients who fail to become afebrile after intravenous immunoglobulin (IVIG) therapy has not been defined. Intravenous methylprednisolone pulse (IVMP) therapy has been reported to be useful for patients who do not respond to IVIG [3, 15]; although, a recent randomized double-blind placebo-controlled trial showed that IVMP is not indicated in initial treatment of KD [8]. Anti-cytokine therapy, especially tumor necrosis factor-α (TNF-α) blockade, is also in the spotlight for a new therapy of refractory KD [1]. In rheumatoid arthritis patients, IVMP was reported to suppress levels of monocyte chemoattractant protein-1 (MCP-1) and TNF-α in serum and synovial fluid [16] and levels in the synovial lining layer [14], but effects of IVMP on cytokine levels in KD are unknown. In this study we sought to determine whether IVMP, compared with additional IVIG, reduces cytokine levels putatively

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involved in coronary artery lesions as well as inflammatory markers in KD patients unresponsive to initial IVIG.

Patients and methods

We performed a prospective, randomized control study to evaluate the efficacy and safety of IVMP, compared with additional IVIG, in KD patients unresponsive to initial IVIG—a single infusion of 2 g/kg of polyethylene glycol-treated human immunoglobulin (Venoglobulin IH; Mitsubishi Pharma Corp., Osaka, Japan) over 24 hours—between January 2001 and May 2003, and the primary results have been reported [7]. At enrollment, the subjects were randomly assigned to either the IVMP group, 30 mg/kg of methylprednisolone per day for 3 consecutive days, or the additional IVIG group, 2 g/kg over 24 hours. The institutional review board approved this study, and informed consent was obtained from the parents of all subjects.

From October 2001 to May 2003, we evaluated laboratory data and cytokine levels in 15 patients, consisting of seven in the IVMP group and eight in the additional IVIG group. Data was evaluated at enrollment (defined as day 1) and on days 4 and 7 after enrollment for interleukin-6 (IL-6), MCP-1, soluble interleukin-2 receptor (sIL-2R), TNF-α, and vascular endothelial cell growth factor (VEGF). By using the quantitative sandwich enzyme immunoassay, we measured the plasma levels of IL-6, MCP-1, TNF-α, and VEGF (QunatiGio for IL-6 and TNF-α, Quantikne for MCP-1 and VEGF; R&D Systems, Inc., Minneapolis, MN, USA) and the serum level of sIL-2R (Cellfree IL-2R Test Kit; Endogen, Inc., Cambridge, MA, USA). A monoclonal antibody specific to each cytokine had been precoated onto a microplate. Standards and samples were pipetted into the wells and the cytokine present was bound by the immobilized antibodies. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific to each cytokine was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to develop light for IL-6, sIL-2R, and TNF-α or color for MCP-1 and VEGF in proportion to the amount of each cytokine bound in the initial step. The development was stopped and the intensity of light or color was measured.

For baseline characteristics and cytokine levels, we analyzed continuous variables with the normal distribution, expressed as mean±SD, by the unpaired t test and those with any nonnormal distribution, expressed as median (interquartile range), by the Wilcoxon rank-sum test. The Fisher exact test was applied for nominal variables. To evaluate changes of laboratory data and cytokine levels, the values at enrollment and at days 4 and 7 were log-transformed and analyzed using repeated measures analyses; the ratios of values at days 4 and 7 to those at enrolment were analyzed similarly. All statistical tests were two-tailed, and $p<0.05$ was considered significant.

Results

At enrollment, there were no significant differences between the IVMP group and the additional IVIG group in baseline characteristics: age was 32±19 months vs. 31±26 (the IVMP group vs. the additional IVIG group); male:female ratio was 5:2 vs. 5:3; number of clinical signs in the diagnostic criteria for KD in terms of patients with 5 signs compared to those with 6 signs was 5:2 vs. 6:2; number of febrile days at the start of initial IVIG was 5 (4–7) vs. 4 (4-4); number of febrile days at enrollment was 9 (8–10) vs. 8 (6–9). Laboratory data and cytokine levels were also similar between the two groups; although, some patients among the IVMP group showed high cytokine levels (Fig. 1): leukocyte count was 12.6 (9.4–15.9) vs. 15.1 (10.7–17.3) × 10^3 /μl; neutrophil count was 9.0 (5.2–12.8) vs. 11.7 (6.0–14.1) × 10^3 /μl; C-reactive protein was 8.0±7.0 vs. 5.6±4.8 mg/dl; IL-6 was 210 (15–670) vs. 102 (59–223) pg/ml ml; MCP-1 was 232 (98–1005) vs. 250 (146–355) pg/ml; sIL-2R was 1860 (686–8310) vs. 1820 (1200–2315) U/ml; TNF-α was 6.6 (2.3–11.9) vs. 5.0 (3.3–6.8) pg/ml; and VEGF was 85 (46–401) vs. 170 (81–210) pg/ml.

Results other than laboratory data and cytokine levels were similar to those in the previous report [7]. The body temperature dropped more rapidly in the IVMP group than in the additional IVIG group ($p=0.01$); the antipyretic effect of IVMP was superior to that of additional IVIG on day 2 ($p=0.04$), but not on day 3 and later. The fraction of febrile patients was significantly lower in the IVMP group than in the additional IVIG group on day 2 (0/7 vs. 3/8, $p=0.03$), but it was similar on day 4 and later (3/7 vs. 4/8) because recurrent fever was found in three patients assigned to the IVMP group and in two patients assigned to the additional IVIG group. There were no significant differences between the two groups in absolute internal diameters of any coronary arteries, their Z scores, or the prevalence of coronary lesions (2/7 vs. 2/8). No patients had coronary aneurysms of 5 mm in diameter in either group. Regarding adverse effects, bradycardia (6/7 vs. 2/8, $p=0.04$) and hyperglycemia (5/7 vs. 0/8, $p=0.01$) were more often in the IVMP group than in the additional IVIG group. There were no significant differences in the fraction of patients with hypothermia (1/7 vs. 0/8), hypertension (6/7 vs. 5/8), embolism (0/7 vs. 0/8), or gastrointestinal bleeding (0/7 vs. 0/8).

The leukocyte and neutrophil counts were significantly increased in the IVMP group than in the additional IVIG group ($p=0.045$ and 0.04, respectively), and both of them were significantly higher in the IVMP group on day 4 ($p=$

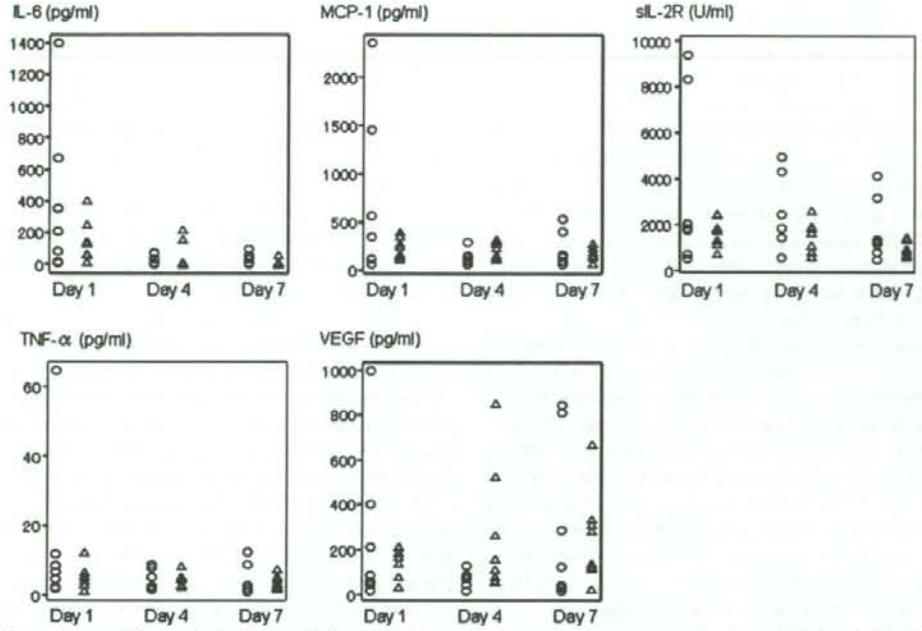

Fig. 1 Changes in cytokine levels in Kawasaki disease patients unresponsive to initial intravenous immunoglobulin (IVIG) therapy who were treated with intravenous methylprednisolone pulse (*circles*) or additional IVIG (*triangles*). Any cytokine levels did not change significantly between the two groups using repeated measures analyses for log-transformed values. *IL-6* interleukin-6; *MCP-1* monocyte chemoattractant protein-1; *sIL-2R* soluble interleukin-2 receptor; *TNF-α* tumor necrosis factor-α; *VEGF* vascular endothelial cell growth factor

Table 1 Ratios of laboratory data and cytokine levels after additional treatment to those at enrollment

	IVMP (n=7)		Additional IVIG (n=8)		p-value
	Day 4	Day 7	Day 4	Day 7	
Laboratory data					
Leucocyte count	1.48±0.72[a]	1.14±0.43	0.84±0.35	1.05±0.40	0.045*
Neutrophil count	1.58±0.93[a]	1.23±0.62	0.65±0.37	0.84±0.45	0.03*
Hemoglobin	0.97±0.03	0.98±0.11	0.96±0.03	0.97±0.06	0.90
Platelet count	1.48±0.30	1.63±0.46	1.57±0.35	2.02±0.82	0.38
C-reactive protein	0.22±0.10[a]	0.37±0.31	0.38±0.17	0.16±0.16	0.02*
Alanine aminotransferase	1.24±0.56	1.76±1.82	0.79±0.35	0.73±0.41	0.21
Albumin	1.02±0.12	1.10±0.21	0.97±0.06	1.06±0.17	0.72
Cytokine levels					
Interleukin-6 (IL-6)	0.08±0.06	0.21±0.21	0.27±0.38	0.11±0.15	0.11
Monocyte chemoattractant protein-1 (MCP-1)	0.53±0.39[a]	0.76±0.39	0.93±0.44	0.61±0.17	0.02*
Soluble interleukin-2 receptor (sIL-2R)	0.72±0.19	0.72±0.39	0.84±0.26	0.62±0.12	0.42
Tumor necrosis factor-α (TNF-α)	0.50±0.27[a]	0.54±0.34	1.01±0.46	0.88±0.39	0.02*
Vascular endothelial cell growth factor (VEGF)	0.73±0.55	2.36±3.28	2.47±2.61	1.90±1.09	0.27

Values are expressed as mean±SD

IVIG intravenous immunoglobulin, *IVMP* intravenous methylprednisolone pulse

* Increases or decreases were significantly greater in the IVMP group than in the additional IVIG group using the repeated measures analysis ($p<0.05$)

[a] $p<0.05$ compared with the additional group using the unpaired t test at day 4 or 7

0.04 and 0.01), but not on day 7. The ratios of leukocyte and neutrophil counts to those at enrollment were significantly increased in the IVMP group (p=0.045 and 0.03, respectively), and both of them were significantly higher in the IVMP group on day 4 (p=0.04 and 0.01), but not on day 7 (Table 1). The C-reactive protein level was significantly decreased in the IVMP group (p=0.01), and it was lower in the IVMP group on day 4 (p=0.03), but not on day 7. The ratio of C-reactive protein level to that at enrollment was significantly decreased in the IVMP group (p=0.02), and it was lower in the IVMP group on day 4 (p=0.03), but not on day 7.

Cytokine levels did not change significantly between the two groups (Fig. 1). However, the ratios of MCP-1 and TNF-α levels to those at enrollment were significantly decreased in the IVMP group compared to the additional IVIG group (p=0.02 and 0.02, respectively), and both of them were significantly lower in the IVMP group on day 4 (p=0.02 and 0.045), but not on day 7 (p=0.07 and 0.83) (Table 1). Although the ratios of sIL-2R, IL-6, or VEGF to those at enrollment tended to be lower in the IVMP group than in the additional IVIG group on day 4, none of them differed significantly between the two groups.

Discussion

In the present study, levels of C-reactive protein, MCP-1, and TNF-α were suppressed more rapidly by IVMP than additional IVIG in KD patients unresponsive to initial IVIG, but this was followed by rebounds after completion of IVMP. In inflammatory sites, MCP-1 facilitates recruitment of monocytes/macrophages, which de novo synthesize and release TNF-α, a pyrogenic cytokine [6]. The changes of these cytokine levels in the IVMP group may thereby explain our previous observation [7] that IVMP, compared with additional IVIG, induced faster but temporary resolution of fever. A rise in the counts of leukocyte and neutrophil by IVMP in our study is to be expected, because the increasing effect of steroids on neutrophil of peripheral blood is well known and dose dependent [11]. In KD patients receiving IVMP therapy, C-reactive protein levels instead of leukocyte and neutrophil counts should be used as inflammatory markers.

The stronger suppression of MCP-1 and TNF-α levels by IVMP is noteworthy for prevention of coronary artery lesions. It was shown that MCP-1 was expressed at the sites of coronary arteritis of fatal KD patients [12], and that the expression of MCP-1 genes persisted or was increased into the convalescent phase in KD patients with coronary artery lesions [13]. It was also reported that the serum level of TNF-α in KD patients was higher in patients with coronary artery lesions than in those without coronary artery lesions [5], and that TNF-α was necessary for the development of coronary artery lesions in an animal model of KD [4]. Thus, IVMP may reduce the prevalence of coronary artery lesions, especially if the rebounds are prevented by any subsequent therapies such as oral administration of prednisone [2]. Because initial IVIG plus prednisolone therapy was reported to reduce rapidly cytokine levels without rebounds [10], a normal dose of steroids may be enough for down-regulation of cytokine secretion in KD patients. On the other hand, longer administration of steroids may induce adverse effects including poor coronary artery outcomes, and the efficacy and safety need to be examined.

Our study has some limitations. The small sample size was not adequate for reliable assessment. We did not stratify the subjects by age and sex at enrollment of the randomized control study. Treating physicians, echocardiographers, or patients' families were not blinded, raising the possibility of a bias in interpreting the results.

In conclusion, IVMP may induce rapid reduction of MCP-1 and TNF-α levels and fast defervescence in KD patients unresponsive to initial IVIG; however, some patients had adverse effects such as bradycardia [7] and rebounds of the cytokine levels with recurrent fever after completion of the administration. We therefore agree with the policy of the American Heart Association [9] that steroid treatment should be restricted to children in whom two or more infusions of IVIG have been ineffective. Further investigations are required to determine the appropriate steroid therapy in the future.

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Ⅲ. 循環器疾患－58

心タンポナーデ

Cardiac tamponade

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1 基本病因，発症機序[1~4]

心タンポナーデとは，心膜液(心嚢液)の貯留により心膜腔(心嚢)内圧が上昇し，心腔が圧排され心拍出量が低下する状態である(心嚢液・心嚢のほうが一般的表現と思うが，日本小児科学会の用語集に準拠し，本稿では心膜液・心膜腔と記載する)。原因は，感染，膠原病，腫瘍，尿毒症，外傷，薬剤，医原性(心臓カテーテル検査，心臓外科手術，中心静脈ライン留置)などさまざまである。原因不明の特発性も多い。

2 基本病態[1~5]

臓側心膜(epicardium)と壁側心膜(pericardium)に囲まれた心膜腔に液体が貯留すると，内圧は初め緩徐に上昇するが，心膜の伸展が限界に達すると急上昇し，心タンポナーデが出現する。まず右心系，次に左心系の拡張能が障害され，右房圧・右室拡張期圧・左房圧・左室拡張期圧がすべて心膜腔内圧と等圧になり，体静脈還流が減少するため心拍出量が低下する。

心膜腔内圧の上昇には，心膜液の絶対量だけでなく，貯留の速度や心膜の硬さも関与する。心膜液が外傷性の出血などで急速に貯留した場合は，少量でも心タンポナーデとなる。一方，炎症・腫瘍などで緩徐に貯留した場合は，大量に貯留するまで心タンポナーデは発症しない。

心タンポナーデでは，呼吸性の両心室の相互作用が強調される(図1)。心腔内の血流量は，吸気時では胸腔内圧・心膜腔内圧が低下するため，右心系で増加し左心系で減少し，呼気時では胸腔内圧・心膜腔内圧が上昇するため，右心系で減少し左心系で増加する。この呼吸性変動は正常では軽度であるが，心タンポナーデでは心腔全体の容量が制限されるため高度となる(吸気時に右室容積が増大した場合，自由壁の偏位は制限されるので心室中隔がより偏位し，左室容積の減少が顕著となる)。この結果，吸気時の収縮期血圧が呼気時より大幅(>10 mmHg)に低下する奇脈(paradoxical pulse)という現象が生じる。

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3 病態生理からみた臨床症候[3]

1. 自覚症状

肺うっ血による呼吸困難・咳，心膜液貯留による胸部圧迫感，心外膜炎による胸痛，腹部内臓うっ血による嘔気・腹痛，心拍出量低下による倦怠感・動悸などの症状がみられ，とくに呼吸困難が高率である(感度88%)。乳幼児では，顔色不良，不機嫌など非特異的症状を呈する。

2. 理学所見

体静脈圧が上昇するため頸静脈の圧上昇と怒張(感度76%)，浮腫，肝腫大を認める。頸静脈波(著明なx谷を示す)は最近あまり診断に用いられない。肺うっ血による多呼吸もみられる(感度80%)。心拍出量が減少するため，頻脈(感度77%)となり血圧が低下(感度26%)する。前述の機序に基づき，吸気時の血圧が低下する特徴的な奇脈を認めるが(感度82%)，呼吸が速い乳幼児では判定が容易ではない。心膜液の貯留により心音は減弱化し(感度28%)，心膜摩擦音を聴取することもある。血圧低下，頸静脈圧上昇，心音減弱を心タンポナーデのBeck's triadとよぶが，必ずしも三つの徴候がそろう訳ではない。

4 病態生理からみた診断のための臨床検査

1. 心エコー[5~7]

心タンポナーデを疑った際は直ちに行うべき検査であるが，臨床所見もあわせて診断しなければ

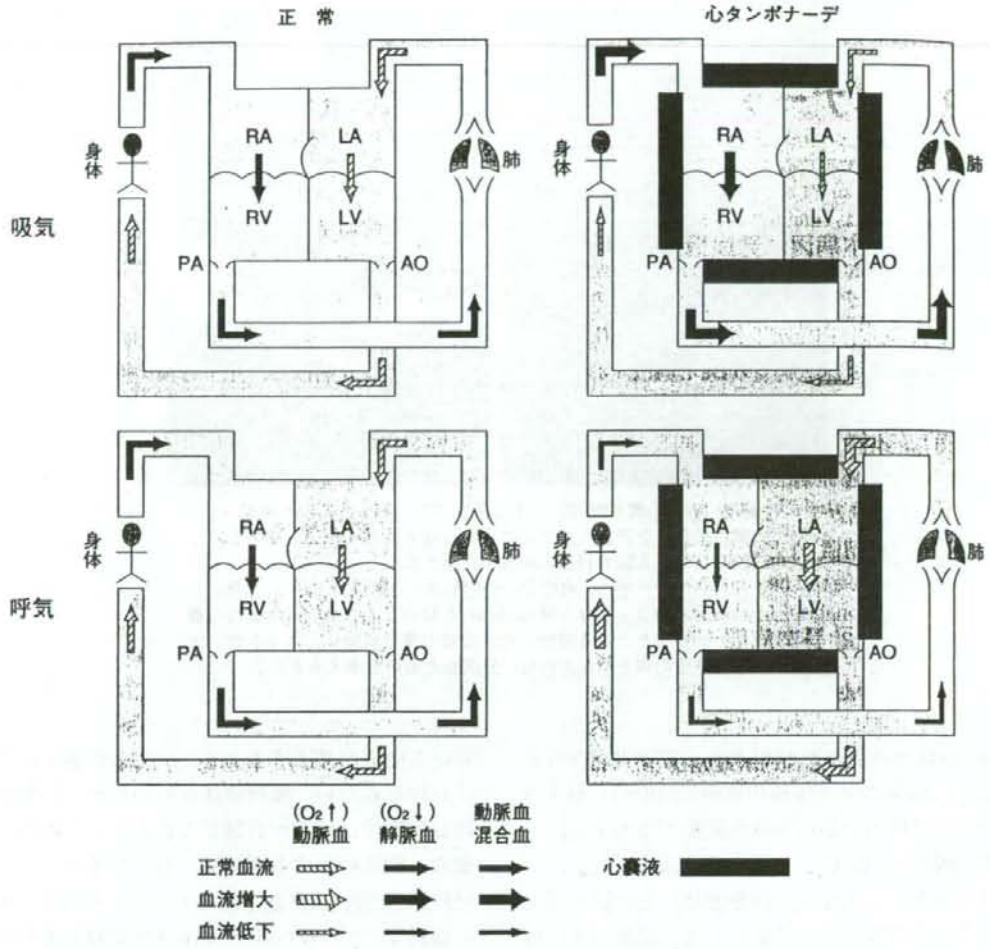

図1 心タンポナーデにおける奇脈の血行動態

心腔内の血流量は，吸気時では胸腔内圧が低下するため，右心系で増加し左心系で減少する。呼気時では胸腔内圧が増加するため，右心系で減少し左心系で増加する。このような呼吸性変動は正常では軽度である(左：中隔の軽度の偏位で示す)。心タンポナーデでは，心嚢内圧の増加により心腔全体の容量が制限されるため，呼吸性変動が強調される(右：中隔の高度の偏位と血流量の矢印の変化で示す)。この結果，吸気時の収縮期血圧が呼気時より大幅に低下する奇脈という現象が生じる。

ならない。

1) 心膜液貯留

心膜腔内にエコーフリースペースが出現する。大量の貯留時には心臓が周期性の振子様運動(swinging heart)を呈する。

2) 右房・右室の虚脱(collapse)(図2)

心膜腔内圧の上昇により低圧の右心系が圧排され，拡張末期・心房収縮期に右房の虚脱，拡張早期に右室流出路の虚脱が認められる。心タンポナーデの診断上，もっとも重要な所見であり，右房の虚脱は感度100%，特異度82%で，全心周期の34%を超える際は感度100%，特異度94%と報告されている。右室の虚脱は，右室肥大などの影響を受けるため，感度は劣るが特異度は高い。進行すると左心系も圧排される。

3) ドップラー法による血流の変化

奇脈と同様の機序(図1)により，三尖弁の右室流入波形(≧25%)と僧帽弁の左室流入波形(≧