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Original Article

Safety and efficacy of palivizumab prophylaxis in children with congenital heart disease*

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Abstract

Background: Infants with congenital heart diseases (CHD) are at high risk for Respiratory syncytial virus (RSV) infection, which causes severe respiratory distress. Palivizumab, an anti-RSV monoclonal antibody, was licensed in the USA, Europe and Canada, and a large-scale placebo-controlled double-blind test in these countries confirmed its efficacy and safety. A survey using questionnaires to assess usage, prophylactic efficacy, and safety of palivizumab in Japanese infants and young children with CHD was conducted.

Methods: The survey was conducted between October 2002 and March 2003. The questionnaire asked for patients' characteristics, presence of CHD, underlying diseases, starting date and number of injection, adverse events, correlation between adverse events and treatment with palivizumab, and evaluation of efficacy.

Results: In total, 108 infants were reported from 61 institutions. A total of 60 of the 108 infants evaluated without major non-cardiac complications received intramuscular injection of 15 mg/kg per month of palivizumab in a manner not consistent with approved indications for this drug. A total of 43 cases (39.8%) had complexed CHD, while 64 cases (59.3%) had the first injection in October or November. The average number of injections was 3.0 ± 1.4. Seven children (6.5%) had notable respiratory infections confirmed by positive test for RSV antigen, and five (4.6%) were hospitalized. No children died nor received mechanical ventilation. The number of adverse events was nine in five cases. There was no significant relationship between adverse events and treatment with palivizumab.

Conclusion: Palivizumab is well-tolerated, fairly effective and safe in preventing severe RSV infection in infants and young children with CHD.

Key words congenital heart disease, monoclonal antibody, palivizumab, respiratory syncytial virus.

Respiratory syncytial virus (RSV) is a major causative agent of airway tract infection, including lower respiratory tract infections such as pneumonia and bronchiolitis, in infants and young children.[1,2] RSV infection may be severe in premature infants[3] and children with underlying diseases such as bronchopulmonary dysplasia (BPD)[4] and congenital heart disease (CHD),[5–7] and in some patients may have a fatal outcome. Lower respiratory tract infection due to RSV is currently treated with conservative treatment, such as oxygen inhalation, fluid replacement and administration of bronchodilators. Ideal methods of prevention and treatment of RSV infection in this population have long been investigated.[8]

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Palivizumab (Synagis, Abbott Japan Co. Ltd, Osaka, Tokyo) is an anti-RSV humanized monoclonal antibody that was approved as the first drug in Japan for prevention of severe lower respiratory tract disease due to RSV infection. This RSV-specific IgG monoclonal antibody was approved to be indicated for infants with a history of premature birth at ≤35 weeks of gestation and infants with BPD as a preventive agent during the peak period of RSV infection. This drug has been reported to decrease the incidence of these high-risk infants who were hospitalized due to RSV infection by approximately 55%.[9,10] In Japan, palivizumab has been given to high-risk infants with officially indicated conditions since October 2002, but treatment for infants with CHD, a non-approved, 'off-labeled' condition, is not indicated. We conducted a questionnaire survey of institutions selected for pediatric cardiology in which palivizumab was used during the last peak period of RSV infection to evaluate the use of this drug during its first season. In this report, the use of palivizumab

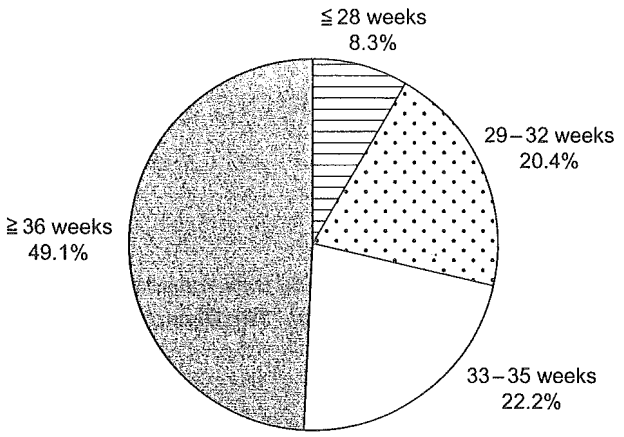

Fig. 1 Percentage of infants receiving palivizumab by length of gestational age.

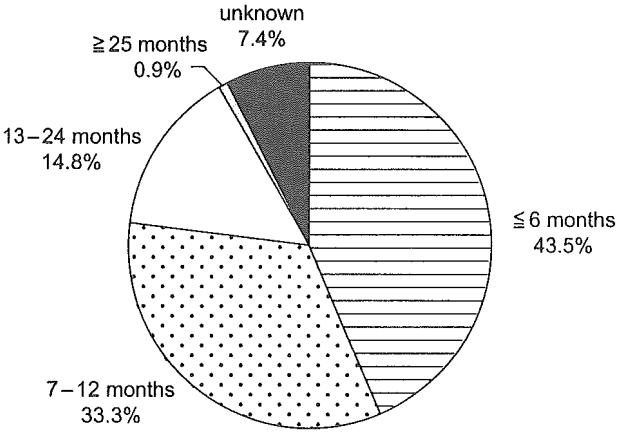

Fig. 2 Age at first administration of palivizumab.

in patients with CHD as well as the clinical characteristics of these infants and the incidence of hospitalization due to RSV infection are described.

Methods

A total of 476 institutions in which palivizumab was used were asked to report the following data in infants using palivizumab:

1 Patient backgrounds: initials, gender, length of gestation at age, birthweight, and age (in months) at first administration;
2 Type of CHD: if present, the presence/absence of cyanosis, pulmonary congestion and pulmonary hypertension;
3 Type of underlying diseases other than CHD and risk factors such as premature birth and bronchopulmonary dysplasia;
4 Timing of initial administration, total number of doses;
5 Type of events due to injection;

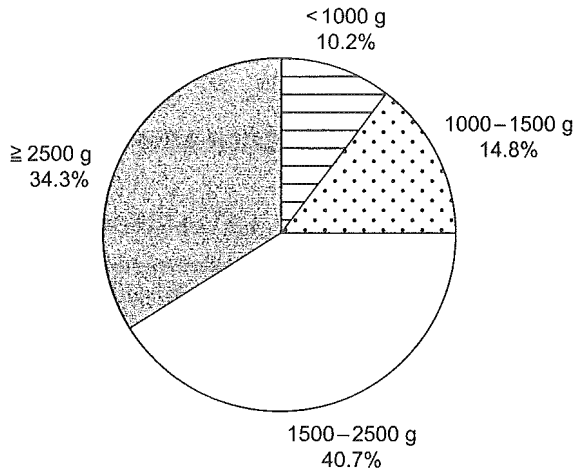

Fig. 3 Percentage of infants receiving palivizumab by birthweight.

6 Causal relationship between the event and treatment;
7 Efficacy rating.

Physicians were instructed to report all cases of palivizumab treatment in infants with CHD regardless of disease severity.

Results

The questionnaire revealed that 61 institutions (12.8% of centers surveyed) treated 108 infants with CHD with palivizumab.

Characteristics of infants

The 108 infants with CHD included 68 males (63%) and 40 females (37%). Gestational age at birth was ≤28 weeks in nine infants (8.3%), 29–32 weeks in 22 (20.4%), 33–35 weeks in 24 (22.2%), and ≥36 weeks in 53 (49.1%; Fig. 1). A total of 55 children (50.9%) met the currently approved indications for this drug, that is, infants with a history of premature birth at ≤35 weeks of gestation. Age at first administration of palivizumab was <6 months in 47 infants (43.5%), 7–12 months in 36 (33.3%), 13–24 months in 16 (14.8%), and other or unknown in nine (8.3%), ranging between 0–32 months, with a median age of 7 months (Fig. 2). Birthweight was <1000 g in 11 infants (10.2%), 1000–1500 g in 16 (14.8%), 1500–2500 g in 44 (40.7%), and ≥2500 g in 37 (34.3%; Fig. 3): low-birthweight infants accounted for a substantial percentage of the infants reported.

Descriptions of congenital heart disease

Table 1 shows the types of CHD in the 108 children evaluated. Patients with complexed heart disease accounted for the largest percentage (39.8%). Patients with ventricular

Table 1 Number of patients receiving palivizumab by type of congenital heart disease

Condition	*n*	(%)	Number of present approved indication
Ventricular septal defect and related conditions	23	21.3	14
Coarctation of the aorta	12	11.1	2
Atrial septal defect	10	9.3	6
Tetralogy of Fallot	6	5.6	3
Hypoplastic left heart syndrome	4	3.7	0
Pulmonary stenosis	4	3.7	1
VSD/PA	3	2.8	1
Aortic stenosis	3	2.8	1
Mixed heart malformation	43	39.8	17
Total	108	100.0	

PA, pulmonary artesia; VSD, ventricular septal defect.

Table 2 Number of patients receiving palivizumab by major clinical manifestation

Condition	*n*	(%)	Number of present approved indication
Cyanosis only	14	13.0	8
Pulmonary congestion alone	8	7.4	6
Pulmonary hypertension alone	8	7.4	2
Cyanosis + pulmonary congestion	7	6.5	2
Cyanosis + pulmonary hypertension	6	5.6	3
Pulmonary congestion + pulmonary hypertension	15	13.9	6
Cyanosis + pulmonary congestion + pulmonary hypertension	19	17.6	3
Absent	31	28.7	6
Total	108	100.0	

septal defect (VSD), coarctation of the aorta (CoA), atrial septal defect (ASD) or tetralogy of Fallot (TOF) were also treated with palivizumab. Table 2 shows the prevalence of signs/symptoms of CHD. Cyanosis was observed in 27 infants (25.0%), pulmonary congestion in 23 infants (21.3%), and pulmonary hypertension in eight infants (7.4%). In total, 19 infants (17.6%) had all three of these conditions, while 31 infants (28.7%) had none of them.

Timing and number of doses

About 80% of the evaluated children received the first administration of palivizumab during the first 3 months from 1 October through 31 December 2002 of the peak period of RSV infection in Japan: 24 children (22.2%) received the first dose in October, 40 (37.0%) in November, and 23 (21.3%) in December. The average number of doses was 3.0 ± 1.4 (mean ± standard deviation) for the infants evaluated, including those receiving more doses after answering of the questionnaire.

Efficacy of palivizumab and adverse events

During the period of treatment with palivizumab, RSV infection was confirmed in seven (6.5%) of the 108 patients evaluated by positive test for RSV antigen, and five infants (4.6%) were hospitalized. This incidence was almost identical to that of hospitalization (5.3%) due to RSV infection in patients with CHD in Europe and the USA, although a direct comparison in studies with different designs is not appropriate. Profiles of patients hospitalized due to RSV infection are presented in Table 3.

Five patients (Table 4) experienced a total of nine adverse events including fever (three events), rhinitis,[1] vomiting,[2] dysphoria,[1] dyspnea[1] and supraventricular tachycardia (SVT;[1] Table 5). Causal relationship to palivizumab was ruled out for all events except those of dysphoria and dyspnea. These two events were observed in an infant with complexed CHD and other complications, and their causal relationships with palivizumab are unknown. No death associated with RSV infection nor with the palivizumab injection.

Discussion

RSV is a major causative agent of airway infection which can lead to respiratory distress in infants and young children. Primary infection with RSV occurs by 12 and 24 months of age in about 60 and 100% of children, respectively.[1,2,11] Reinfection with RSV is also frequent because acquired immunity to RSV is incomplete.[11] RSV infection is usually severe in premature infants and infants with chronic lung

Table 3 List of hospitalized patients' profile

Case No. (week)	GA (g)	BW (m)	Age	Sex	HD	Symptom	Other condition	Time of injection	Number of injections
1	32	1592	NR	F	ASD	pulmonary congestion	Tracheomalacia	02.11–03.1	3
2	37	1575	7	M	AS	none	CLD	02.12	1
3	38	3018	16	M	TOF	pulmonary congestion pulmonary hypertension	Trisomy 9 & 21 None	02.10–02.11	2
4	34	1690	NR	F	VSD	pulmonary congestion pulmonary hypertension	Tracheomalacia	02.11–03.3	5
5	32	1826	NR	M	ASD VSD PDA	cyanosis pulmonary congestion pulmonary hypertension	CLD	02.9–03.2	6

AS, Aortic stenosis; ASD, Atrial septal defect; BW, birthweight; CLD, chronic lung disease; GA, gestational age; HD, heart disease; NR, not recorded; PDA, patent ductus arteriosus; TOF, Tetralogy of Fallot; VSD, ventricular septal defect.

Table 4 List of patients with adverse events

	GW	Sex	Birthweight (g)	Condition(s)	Number of injection(s)	Adverse event(s)
1	40w	M	2806	VSD, CoA complex	5	Fever, vomiting
2	36w	M	2016	DORV	1	Fever, rhinitis, vomiting
3	38w	M	2234	VSD	1	Fever, SVT
4	36w	M	2190	PDA, CoA	2	Dyspnea
5	31w	M	1578	VSD, PPA, MAPCA	2	Dysphoria

CoA, Coarctation of the aorta; DORV, double outlet right ventricle; MAPCA, major aorto pulmonary collateral arteryPDA, patent ductus arteriosus; PPA, pure pulmonary artesia; SVT, supraventricular tachycardia; VSD, ventricular septal defect.

Table 5 List of adverse events

	No. of events related	No. of events not related	Unknown	No. of present approved indication
Fever	3	3		0
Rhinitis	1	1		0
Vomiting	2	2		0
Dysphoria	1		1	1
Dyspnea	1		1	1
Supraventricular tachycardia	1	1		0

disease, including those with BPD. It has been reported that premature infants account for 25–30% of infants hospitalized due to RSV infection,[1,3] and that RSV infection is observed in 60% of infants with BPD who are hospitalized due to lower respiratory tract disease.[4] RSV infection may be severe also in high-risk infants with CHD[5–7] and infants with immunodeficiency syndrome.[12] In these high-risk states, RSV infection may result in a fatal outcome due to severe cardiopulmonary dysfunction.

Palivizumab, an anti-RSV monoclonal antibody released in Japan in May 2002, is an IgG antibody that inactivates RSV by binding specifically to RSV fusion (F) protein.[13] Currently, palivizumab is approved for use to prevent severe lower respiratory tract disease due to RSV infection in infants with a history of premature birth at ≤35 weeks of gestation and infants with BPD, at a dose of 15 mg/kg every 30 days. However, palivizumab is not officially approved for infants and young children with CHD in Japan. Management of RSV infection in this high-risk population is not sufficient because of current limitations of indications. RSV infection may result in a delay to elective heart surgery in a substantial number of infants.

This questionnaire revealed 108 cases of treatment with palivizumab in infants with CHD in 61 institutions. The characteristics of the infants evaluated suggest that physicians selected infants who met, in terms of gestational age at birth and age at first administration, the current indications for treatment with palivizumab. Since palivizumab is an expensive drug and use for patients with CHD is not covered by Japanese national health insurance, physicians appear to have

prescribed palivizumab to patients with CHD by including them within the range of approved indications. However, off-label use of palivizumab was reported for 60 children. This reflects the strong concern regarding the risks of RSV infection in this population and the importance of prevention of RSV infection, a major factor hindering treatment of CHD. CHD must be included in the indications of palivizumab in order to ensure optimal treatment in this population. The range of bodyweight at birth in this survey is consistent with the finding that many of the infants evaluated had a history of preterm birth and that CHD is more prevalent in low-birthweight infants.[14–17]

Infants with complexed CHD accounted for the largest percentage of patients evaluated, and percentages of infants with VSD, CoA, ASD and TOF were also high. These five diseases were together reported in 87% of the patients evaluated. Many children with these conditions are awaiting surgical correction. RSV infection in such infants may cause severe respiratory distress which may prevent optimal timing of surgery or may even result in an unexpected surgical outcome. In some cases in this survey, palivizumab was given before surgery to prevent severe RSV infection and after surgery when residual pulmonary hypertension, a condition possibly leading to severe RSV infection, was observed.

Treatment with palivizumab was started in late fall or early winter (October–December) in many institutions and was continued until 1 month after surgery or until the end of the RSV communicable season.[18,19] In order to ensure prevention of severe RSV infection, the serum palivizumab level should already be elevated at the beginning of the RSV season and should be maintained within the effective concentration throughout this season.[20] Since sufficient serum concentration of palivizumab should be achieved during the 3 month period between December and February, when RSV epidemics may peak, prompt intervention is preferable. Initial administration should be performed between late October and early November, although geographic variation in the RSV season should be considered in the timing of this administration.

Hospitalization due to RSV infection was evaluated as a measure of reliable efficacy of palivizumab treatment. In this survey, five of the 108 (4.6%) reported patients were hospitalized due to RSV infection. In a study of infants with CHD in Europe and the USA, incidence of hospitalization due to RSV infection in the palivizumab group was 5.3%, which represented a 45% reduction compared with the placebo group ($P < 0.003$).[21] Although direct comparison between a questionnaire survey and a randomized controlled study is not appropriate, incidence of hospitalization in children with CHD due to confirmed RSV infection in our survey was similar to the above study in Europe and the USA, and the reduced incidence of hospitalization determined in our survey may be due in large part to the use of palivizumab. The incidence of death associated with RSV infection is also less in the treatment group.[22]

Regarding safety, a total of nine adverse events were reported in five children. Causal relationship with treatment seems to be ruled out for all events except dysphoria and dyspnea. The latter two events were observed in an infant with severely complex malformations, and their causal relationships with palivizumab are unknown. Adverse events in patients receiving palivizumab should be assessed considering the characteristics of patients who have a history of premature birth or high-risk conditions such as BPD and CHD.[23]

In our survey, 60 of the 108 infants and young children evaluated were treated with palivizumab for reasons not consistent with approved indications. Clinical experience with palivizumab in children with CHD has been presented in scientific meetings during the last 2 years[24,25] and the use of palivizumab has been increased. The efficacy and safety of palivizumab prophylaxis in children with CHD were demonstrated in large-scale clinical studies in Europe and the USA.[17,25–27]

We conclude that palivizumab is safe and useful in minimizing the incidence of RSV infection in infants and young children with CHD. The results of a well-designed prospective study of the efficacy and safety of palivizumab in patients with CHD to be started this coming RSV season are awaited.

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Appendix I. The pediatric cardiologists who cooperated in this study and their institutions

H. Tomita (Muroran City Hospital); N. Takahashi and Y. Ota (Tenshi Hospital); T. Sato (Iwamizawa City Hospital); M. Fukuda (Iwate Medical University Memorial Heart Center); U. Fukuoka (Ota Nishinouchi Hospital); N. Takahashi and T. Furuta (Saitama City Hospital); S. Tanabe (Chiba Prefectural Cardiovascular Center); J. Shimizu (Tsuchiura Kyodo General Hospital); M. Wada (Tokyo Dental College Ichikawa General Hospital); A. Umeda (Showa General Hospital); H. Yoda (Japanese Red Cross Medical Center); S. Ogawa (Nippon Medical School); K. Tamura (Toho University Omori Hospital); M. Hida (Keio University Hospital); H. Sato (Juntendo University Hospital); M. Shimizu (Metropolitan Bokuto Hospital); T. Yoda (St. Marianna University Hospital); M. Aikyo (St. Marianna University Yokohama City West Hospital); S. Kunishima (Hiratsuka City Hospital); S. Fukuda (Nagoya City University Hospital); N. Nagai (Okazaki City University); M. Ikoma (Japanese Red Cross Nagoya First Hospital); Y. Tanaka (Shizuoka Children's Hospital); M. Miyaji (Shizuoka saiseikai Hospital); K. Sugiyama (Mie Prefectural General Medical Center); S. Ogaki (Ikeda City Hospital); S. Hayashi (Sakai City Hospital); K. Wada (Osaka University Hospital); H. Kanaoka (Osaka Red Cross Hospital); M. Yoshibayashi (Kinki University Nara Hospital); K. Nishiike (Aizenbashi Hospital); K. Takemoto (Hannan Chuo Hospital); S. Toriuchi (National Cardiovascular Center); Y. Yoshida (Higashiosaka

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Lack of Human Herpesvirus 8 Infection in Lungs of Japanese Patients with Primary Pulmonary Hypertension

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Samples of lung tissue, taken at autopsy, from 10 Japanese patients with primary pulmonary hypertension (PPH) and samples of lung tissue from 12 Japanese patients with secondary pulmonary hypertension were tested for the presence of human herpesvirus 8 (HHV-8). All samples from patients with PPH contained plexiform lesions around pulmonary arterial vessels, but immunohistochemistry failed to detect the HHV-8–encoded latency-associated nuclear antigen. HHV-8 DNA could not be amplified by polymerase chain reaction for the HHV-8–encoded K1 and $KS330_{233}$ genes in any sample. These data suggest that HHV-8 infection is not associated with PPH in Japanese patients.

Primary pulmonary hypertension (PPH) is a rare disease that leads to severe right heart failure, which is characterized histologically by vascular lesions in the lung and the proliferation of endothelial cells and smooth muscle cells in the pulmonary arterial walls; these conditions then induce luminal obstruction, resulting in elevation of pressure in the pulmonary arteries. Some cases of PPH are associated with genetic mutations in bone morphogenetic protein receptor 2 (BMPR2) [1]. Recently, human herpesvirus 8 (HHV-8)—also known as Kaposi sarcoma (KS)–associated herpesvirus—was identified, by polymerase chain reaction (PCR), in 10 of 16 samples of lung tissue from patients with PPH, and the expression of latency-associated nuclear antigen (LANA), encoded by HHV-8, was detected, by immunohistochemistry, in the vascular "plexiform" lesions in these patients' lungs, suggesting an association between HHV-8 and the pathogenesis of PPH [2]. Because only 2 of these 10 HHV-8–positive patients had BMPR2 mutations, HHV-8 infection did not correlate with BMPR2 mutations in these patients [2].

HHV-8 is categorized as a gamma herpesvirus [3], and the seroprevalence of HHV-8 varies geographically. HHV-8 has a high seroprevalence in the general population in African countries (40%) and in southern European countries (10%), but a low prevalence has been suggested in the United States (3%) and in Asian countries, including Japan (1.4%) [4]. HHV-8 has been detected in KS, primary effusion lymphoma (PEL), and some cases of multicentric Castleman disease (MCD) [3]. HHV-8–encoded LANA is always expressed in the cells of KS and PEL, suggesting an HHV-8 infection in the latent phase. In contrast, not only LANA but also other lytic antigens of HHV-8 are expressed in the cells of MCD, implying that it has a different pathogenesis than do KS and PEL [5]. LANA, however, plays an important role in the pathogenesis of KS and PEL [3]. The histological features of the plexiform lesions of PPH—proliferation of spindle-shaped cells with vascular slits—resemble the histological features of KS [2]. Although mutations of BMPR2 have been detected in some isolated cases of PPH and in some cases of familial PPH in Japan [6], the pathogenesis of most cases of PPH is still unknown. In the present study, we investigated the presence of HHV-8 in the lung tissue from 10 Japanese patients with PPH and from 12 Japanese patients with secondary pulmonary hypertension (SPH).

Subjects, materials, and methods. During 1981–2003, 10 Japanese patients with PPH underwent autopsy at Toho University Hospital in Tokyo, Japan, and samples of their lung tissue were taken for analysis; samples of lung tissue were also taken from 12 Japanese patients, living in the Tokyo area, who had SPH and were not infected with HIV (table 1). The mean age of the patients with PPH was 23.4 years (range, 0–51 years), and the mean age of the patients with SPH was 31.4 years (range, 0–83 years). Immunohistochemistry was performed to investigate the expression of LANA on cells of lung tissue, as described elsewhere [5]. A rabbit polyclonal antibody to LANA (dilution, 1:3000 [5]) and a rat monoclonal antibody to LANA (dilution, 1:3000; Advanced Biotechnologies) were used as primary antibodies. Samples of KS tissue obtained from additional patients were used as positive controls. For PCR analysis, DNA was extracted from samples of lung tissue that were fixed in formalin and embedded in paraffin. DNA from a sample of KS tissue obtained from an additional patient was used as a positive control, and DNA from a sample of healthy skin obtained from an additional patient was used as a negative control [5]. PCR

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Table 1. Characteristics of the study population and results of polymerase chain reaction (PCR) and immunohistochemistry (IHC).

Patient	Age, years	Sex	No. of paraffin blocks tested	Diagnosis	K1, by nested PCR	$KS330_{233}$, by PCR	β-globin, by PCR	No. of plexiform lesions	LANA, by IHC
1	29	M	3	PPH	–	–	+	124	–
2	41	M	3	PPH	–	–	+	50	–
3	0	F	3	PPH	–	–	+	103	–
4	39	F	3	PPH	–	–	+	81	–
5	0	F	1	PPH	–	–	+	18	–
6	21	F	5	PPH	–	–	+	119	–
7	16	F	3	PPH	–	–	+	24	–
8	24	M	3	PPH	–	–	+	110	–
9	13	F	2	PPH	–	–	+	41	–
10	51	F	2	PPH	–	–	+	42	–
11	61	M	1	SPH (ASD)	–	–	+	10	–
12	51	M	1	SPH (gastric cancer)	–	–	+	30	–
13	0	F	1	SPH (ECCD)	–	–	+	6	–
14	1	M	1	SPH (TGA)	–	–	+	20	–
15	1	F	2	SPH (DS, ASD, VSD)	–	–	+	39	–
16	8	M	1	SPH (ECCD)	–	–	+	0	–
17	0	F	1	SPH (DS, ASD, VSD)	–	–	+	0	–
18	83	F	1	SPH (RA)	–	–	+	21	–
19	47	F	2	SPH (ASD)	–	–	+	102	–
20	59	M	1	SPH (MI)	–	–	+	15	–
21	18	F	1	SPH (ASD, VSD)	–	–	+	6	–
22	48	M	1	SPH (ALS)	–	–	+	48	–

NOTE. For patients with secondary pulmonary hypertension (SPH), the primary condition (or related conditions) is listed in parentheses. ALS, amyotrophic lateral sclerosis; ASD, atrial septal defect; DS, Down syndrome; ECCD, endocardial cushion defect; LANA, latency-associated nuclear antigen; MI, myocardial infarction; PPH, primary pulmonary hypertension; RA, rheumatoid arthritis; TGA, transposition of great arteries; VSD, ventricular septal defect; –, not detected; +, detected.

was performed, as described elsewhere [7], to detect the $KS330_{233}$ gene of HHV-8 (HHV-8–encoded ORF26). Nested PCR was performed to detect the K1 gene of HHV-8. For the first round of nested PCR, the external primer pair K1SF (forward primer, 5′-TTGTGCCCTGGAGTGATT-3′) and K1SR (reverse primer, 5′-CAGCGTAAAATTATAGTA-3′) was used to amplify a 363-bp fragment of the K1 gene of HHV-8 [8]. The conditions for the first round of PCR were 1 cycle at 94°C for 4 min, followed by 35 cycles at 94°C for 1 min, 58°C for 1 min, and 72°C for 2 min. For the second round of PCR, the inner primer pair K1VR1F1 (forward primer, 5′-TTGCCAATATCCTGGTATTGC-3′) and K1VR1R1 (reverse primer, 5′-CAAGGTTTGTAAGACAGGTTG-3′) was used to amplify a 162-bp fragment of the K1 gene; the same conditions as in the first round of PCR were used. The β-globin gene was amplified as a control, as described elsewhere [7].

Results. To investigate whether HHV-8 was present in the samples of lung tissue from patients with PPH, we first performed immunohistochemistry to detect LANA. Staining with hematoxylin-eosin revealed that all samples from patients with PPH had characteristic plexiform lesions in their pulmonary arteries (figure 1). In samples from patients with PPH, 18–124 plexiform lesions were tested (table 1). Some samples from patients with SPH also had plexiform lesions. Immunohistochemistry by use of 2 antibodies to LANA revealed that LANA was not present in any sample obtained from patients with either PPH or SPH (table 1), whereas LANA was detected as a dot-like nuclear staining pattern in samples of KS tissue obtained from control patients (figure 1). Although sclerosing lesions and proliferation of endothelial cells and smooth muscle cells around vessels were observed in the plexiform lesions, LANA was not present. To confirm the results of the immunohistochemistry, we extracted DNA from the samples of lung tissue and performed PCR. Both PCR amplification for the $KS330_{233}$ gene of HHV-8 and nested PCR amplification for the K1 gene of HHV-8 failed to detect HHV-8 DNA in all samples (table 1). The control gene β-globin was detected in all samples. These data and the results of the immunohistochemistry suggest that the patients with PPH did not have HHV-8 infection.

Discussion. In the present study, we have demonstrated that 10 Japanese patients with PPH and 12 Japanese patients with SPH did not have HHV-8 infection. Although we used testing procedures similar to those employed by Cool et al. [2, 9]—immunohistochemistry and PCR—our results were completely different from theirs.

Patients with PPH are found worldwide. Only 50% of patients

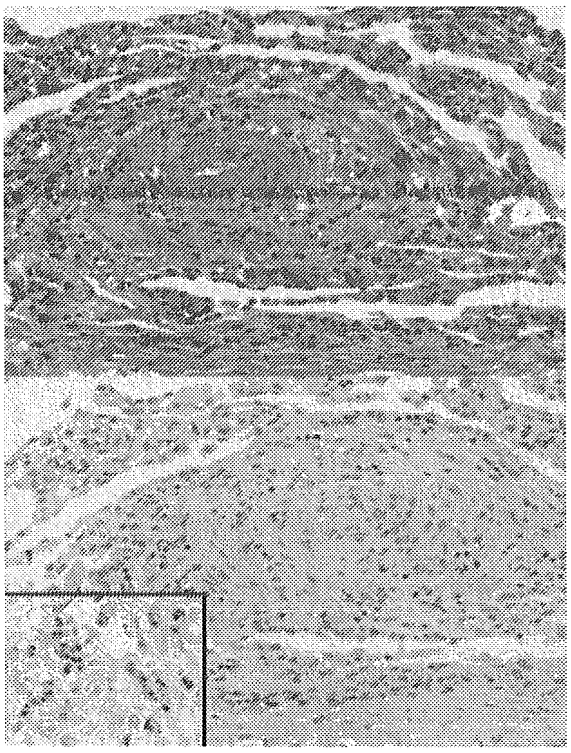

Figure 1. Plexiform lesions in lung tissue from a patient with primary pulmonary hypertension. *Top,* Lung tissue stained with hematoxylin-eosin. *Bottom,* Detection of latency-associated nuclear antigen (LANA) by immunohistochemistry. *Inset,* Expression of LANA (dot-like nuclear staining pattern) in Kaposi sarcoma from a positive control patient.

with familial PPH have BMPR2 mutations, and no BMPR2 mutations have been detected in patients with isolated cases of PPH. Because HHV-8 was not detected in 6 of the 16 patients with PPH whom Cool et al. studied, the authors suggested that BMPR2 mutations and HHV-8 infection were not correlated [2]. The present study has demonstrated that all 10 Japanese patients with PPH were negative for HHV-8 infection. Although we were unable to examine the seropositivity of the patients with PPH, in a study published elsewhere, we demonstrated that the seroprevalence of HHV-8 was low (1.4%) in the general population in Japan [4]. These data suggest that PPH might be induced by causative factors other than HHV-8 infection and BMPR2 mutations. Therefore, it is possible that the pathogenesis of PPH in Japan is different from that of PPH in the United States. Other genetic backgrounds, modifier genes, or other pathogens may be associated with cases of PPH in Japan.

The sensitivity and methods used in the present study, however, were different from those used by Cool et al. [2]. Our immunohistochemistry succeeded in detecting LANA in all cases of KS, regardless of the stage of disease or the patient's HIV infection status, and the results of immunohistochemistry correlated well with those of PCR [5]. Cool et al. detected LANA not only in the cells within plexiform lesions but also in bronchoepithelial cells and in inflammatory cells, including lymphocytes and macrophages [2, 9], but we were not able to detect LANA in any cells of the samples obtained from patients with PPH. LANA has been detected only in the nuclei of KS cells and not in surrounding cells, including epithelial cells, lymphocytes, and macrophages, even in samples of lung tissue from patients with KS [5]. To date, HHV-8 has been detected, by PCR, in patients with various diseases, but immunohistochemistry has yielded positive results only in samples from patients with KS, PEL, MCD, and some solid lymphomas [10, 11]. Recently, a low seroprevalence of antibodies to HHV-8 in patients with PPH in Germany was reported, suggesting that HHV-8 infection is rarely involved in the pathogenesis of PPH [12]. Further studies are required to clarify the strict association between HHV-8 infection and PPH.

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特集　膠原病とその周辺疾患にみられる血管病変―その病態と治療

川崎病の血管病変*

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はじめに

川崎病(KD)は1967年の第一例の報告[1]以来，38年近くが経過した．発見当時，1つのdisease entityとしての特異性が社会的に受け入れられるまでは，とくに乳児結節性動脈周囲炎JPNや溶レン菌感染症などとの区別が論議を呼んだという[2]．以後35年間を経過し，世界の小児科医の認知を得たKDは，日本での患者総数は18万人を越えている．

疫学調査からのデータ

1970年以来KD全国調査が行われてきた．2001～2002年の2年間の患者を対象に実施した第17回全国調査の成績を以下に示す[3]．

2年間の患者数は16,952人であった．平均罹患率は0～4歳人口10万対145.0(男162.7，女126.5)であった．性比は1.35で男が多い．2002年12月末までの総患者数は，合計186,069人で，これまでに1979年，1982年，1986年の3回にわたり全国規模の流行がみられた．

3歳未満のものの割合は全体の67.0%で，家族歴では，同胞例ありの割合は報告患者中1.3%であった．再発例の割合は報告患者中3.6%であった．死亡例は2年間に2人(男2人，女0人)報告され，致命率は0.01%であった．いずれも初診時年齢が1歳未満であった．

1．診　断

定型例83.8%(男84.0%，女83.6%)，不定型例3.0%，容疑例13.2%であった．

(1)定型例

「川崎病診断の手引き　改訂5版(2002年2月に診断の手引きが改訂され，第17回全国調査から改訂5版を使用)」(表1)に示された6つの主要症状のうち5つ以上の症状を伴うもの，不定型例(「確実B」)は4つの症状しか認められなくても，経過中に断層心エコー法もしくは，心血管造影法で，冠動脈瘤(いわゆる拡大を含む)が確認され，ほかの疾患が除外されたものをいう．また，容疑例(「容疑」)は上記のいずれにも合致しないが，主治医がKDの疑いありと診断したものをいう[4]．

(2)主要症状の出現割合

発熱99.3%，眼球結膜充血92.6%，口唇・口腔所見89.3%，不定形発疹88.4%，四肢末端の変化81.9%，頸部リンパ節腫脹68.6%であった．臨床の現場では，類似疾患が時に経験され，また，

* Vasculopathy in Kawasaki disease.

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表1 川崎病診断の手引き(厚生労働省川崎病研究班作成改訂5版，2002年2月改訂，初版1970年9月)

本症は，主として4歳以下の乳幼児に好発する原因不明の疾患で，その症候は以下の主要症状と参考条項に分けられる．

A. 主要症状

1. 5日以上続く発熱(ただし，治療により5日未満で解熱した場合も含む)
2. 両眼球結膜の充血
3. 口唇，口腔所見，口唇の紅潮，いちご舌，口腔咽頭粘膜のびまん性発赤
4. 不定形発疹
5. 四肢末端の変化(急性期)手足の硬性浮腫，掌せきないしは指足末端の紅斑
   (回復期)指先からの膜様落屑
6. 急性期における非化膿性頸部リンパ節腫脹

6つの主要症状のうち5つ以上の症状を伴うものを本症とする．ただし，上記6主要症状のうち4つの症状しか認められなくても，経過中に断層心エコー法もしくは，心血管造影法で冠動脈瘤(いわゆる拡大を含む)が確認され，ほかの疾患が除外されれば本症とする．

B. 参考条項

以下の症候および所見は，本症の臨床上留意すべきものである．

1. 心血管：聴診所見(心雑音，奔馬調律，微弱心音)，心電図の変化(PR・QTの延長，異常Q波，低電位差，ST-Tの変化，不整脈)，胸部X線所見(心陰影拡大)，断層心エコー図所見(心膜液貯留，冠動脈瘤)，狭心症状，末梢動脈瘤(腋かなど)
2. 消化器：下痢，嘔吐，腹痛，胆嚢腫大，麻痺性イレウス，軽度の黄疸，血清トランスアミナーゼ値上昇
3. 血液：核左方移動を伴う白血球増多，血小板増多，赤沈値の促進，CRP陽性，低アルブミン血症，α2グロブリンの増加，軽度の貧血
4. 尿：蛋白尿，沈渣の白血球増多
5. 皮膚：BCG接種部位の発赤・茄皮形成，小膿疱，爪の横溝
6. 呼吸器：咳そう，鼻汁，肺野の異常陰影
7. 関節：疼痛，腫脹
8. 神経：髄液の単核球増多，けいれん，意識障害，顔面神経麻痺，四肢麻痺

備考：

1. 主要症状Aの5は，回復期所見が重要視される．
2. 急性期における非化膿性頸部リンパ節腫脹はほかの主要症状に比べて発現頻度が低い(約65%)．
3. 本症の性比は1.3～1.5：1で男児に多く，年齢分布は4歳以下が80～85%を占め，致命率は0.1%前後である．
4. 再発例は2～3%に，同胞例は1～2%にみられる．
5. 主要症状を満たさなくても，ほかの症状が否定され，本症が疑われる容疑例が約10%存在する．このなかには冠動脈瘤(いわゆる拡大を含む)が確認される例がある．

二次性KDと考えざるを得ないと思われる続発性のKDにも遭遇する[5]．最近ではKawasaki diseaseよりもsyndromeという考え方が欧米では受け入れられてきた．

2. 心障害の頻度

心障害例(急性期：1か月以内)の割合は16.2%(男18.6%，女13.9%)，1か月以後の後遺症の割合は5.0%で，後遺症は急性期に比べて男女とも約1/3に低下していた．心障害(急性期)の種類別の割合は，冠動脈の拡大12.97%，瘤1.96%，弁膜病変1.58%，巨大瘤0.27%，狭窄0.05%，心筋梗塞0.02%であった．

後遺症の割合は報告患者中，冠動脈の拡大3.13%，瘤1.36%，巨大瘤0.29%，弁膜病変0.31%，狭窄0.06%，心筋梗塞0.04%であった．

3. 治療の状況

患者の初診日は第4病日がもっとも多く(23.3%)，退院時病日は第13～15病日がもっとも多く20.1%であった．静注用ガンマグロブリン(IVIG)の治療を受けたものは86.0%(男86.6%，女85.2%)を占めている．1日投与量と使用日数から計算した使用総量は，1,900～2,099mg/kgがもっとも多く70.2%，次いで900～1,099mg/kgが16.5%であった．

血管炎の特徴と病態[6]

KDの血管炎は，Chapel-Hill分類では中型動脈炎に分類されている．冠動脈瘤は近位部，分岐部に多く，時に腋か動脈，腸骨動脈病変などの末梢動脈瘤が合併するが，静脈病変と頭部の脳

動脈病変はきわめて稀である．

〔血管障害の機序・病態〕

急性期KDでは，さまざまな血管作動物質の異常が報告されている．酸化ストレスマーカーである8-isoprostaneも上昇し，IVIG投与により低下する[7]．

1．一酸化窒素nitric oxide(NO)

NOは血中/尿中ともNO代謝物(NOx)が非常に高く，皮膚生検組織の免疫染色の結果からも血管内皮細胞上のeNOSやiNOS発現が亢進している．KDでは冠動脈障害例で有意に高値を示す．

2．Endothelin(ET)

ET-1は，血漿中で健常児の1.5～2.0倍から高くて3.5倍前後にまで上昇している．上昇したETはIVIG治療後や遠隔期ではほぼ正常と同じ程度にまで低下する．

3．接着因子adhesion molecules

多くの接着因子〔E-Selectin，selectin family，Ig super familyのinter cellular adhesion molecule-1(ICAM-1)〕が増加している．皮膚生検所見でもEC上に強く発現しており，血中のsoluble接着因子も増えており，HLA-DRも急性期の血管周囲のマクロファージ，小リンパ球，内皮細胞でも陽性に染色される．皮膚生検所見は多形浸出性紅斑に類似した所見で，本質的には血管炎とは言い切れないが，ICAM-1，endothelial leukocyte adhesion molecule-1(ELAM-1)なども高率に染色される．

4．成長因子growth factors

Vascular endothelial growth factor(VEGF)，PDGFは急性期に増加する．PDGFはマクロファージから生産され，血管周囲のマクロファージ様の細胞で(PDGF-BB)蛋白が発現し，soluble PDGFも増えている．Transforming growth factor-β(TGF-β)は不変ないし低下するとの報告がある．また，VEGFも増強し，血管透過性亢進，冠動脈拡張，albumin低下に関与し，HGFも増加している．血管障害の長期予後に関してもTGF-β，PDGF-A，basic FGFは血管壁で発現が亢進し血管新生angiogenesisや再構築remodelingに影響を及ぼしていると考えられる．

5．Prostanoids(PGs)

トロンボキサン(TXA_2，B_2)，PGD2，PGF2αなどが増えており，どちらかというと血管収縮/血小板凝集亢進に作用している．ほかにもLTD_4，C_4，B_4，E_4などといったロイコトリエンも増加している．PGI_2は急性期に減少しているが，IVIG療法だけで産生が正常に復帰し，内皮細胞機能が元へ戻る．TXB_2はIVIGによって低下し，PGI_2/TXB_2を正常化させPG代謝系を正常に戻す作用がある．Thrombomodulin(thm)は増加し線溶が低下している．とくに冠動脈後遺症症例では冠静脈内でthmが増加し，遠隔期でも29%の症例で増加しているという．

6．そのほかのcytokines

血管障害の契機は，血管内皮細胞ECへの白血球，リンパ球，macrophageの接着に続いて起こる病変部への侵入，Tリンパ球，平滑筋細胞，血小板の活性化と，分泌された多くのcytokine，chemokine，matrix metalloproteinase(MMP)が初期病変形成の主役と成る．単球はMCP-1により内膜へ遊走し，M-CSFによりmacrophageに分化し血管も脆弱性をきたす因子を産生する．活性化Tリンパ球はIFN-γによりmacrophage，EC，SMCを活性化させ，さまざまなgrowth factorsを産生する．KDでは多くのinterleukinの活性亢進が報告されており，接着－遊走－活性化－の過程を形成している(表2)．

7．平滑筋細胞(SMC)とmatrix/protease

Lamininは平滑筋と内皮細胞の間にある基底膜の裏打ち蛋白で基底膜を支える間質の重要な蛋白である．KDでは非常に高く，とくに白血球，好中球，CRPの高い症例とよい相関があり，重症ほどlamininの血中濃度が高い．血中MMP-1，-3，TIMP-1は有意に上昇し，IVIG後はMMP-2/TIMP-1 ratioは低下，MMP-9/TIMP-1 ratioは上昇する傾向があった．また，MMP-3，MMP-9/TIMP-2 ratioは冠動脈異常症例で有意に高いとの報告がある．これらMMPの活性増強によりmatrixの破壊や分解とTIMPによる修復機転が作用していることがうかがわれる．

心臓後遺症の病態と自然歴[8]

1．冠動脈障害(図1)

冠動脈瘤の残存率は，アスピリンやステロイド療法が行われていた1983年度は16.7%，IVIGが

表２　急性期川崎病における分子免疫学的異常[6]

接着因子	
sICAM-1, sL-Selectin, sE-Selectin, sP-Selectin	増加
ICAM-1, ELAM (skin biopsy)	増加
AVCAM, LFA-1 (PMN), L-selectin (Plt)	変化なし
成長因子・サイトカイン	
VEGF, PDGF, HGF	増加
IL-1β, IL-2, sIL-2R, IL-6, IL-8, IL-10	増加
Mac-1 (PMN), MCFS/MCP-1, M-CSF, G-CSF	増加
TNF-α, IFN-γ	増加または変化なし
TGF-β	低下または変化なし
Prostanoids	
TXA_2, TXB_2, PGE_2, PGF2α	増加
LTB_4, LTC_4, LTD_4, LTE_4	増加
PGI_2 (6-keto-PGF1α)	減少
血管作動性物質	
Endothelin-1, hANP, thrombomodulin	増加
$NO3^-$ (serum), NOx (urine)	増加
Biopterine/neopterine ratio	増加
$NO2^-$ (serum)	変化なし

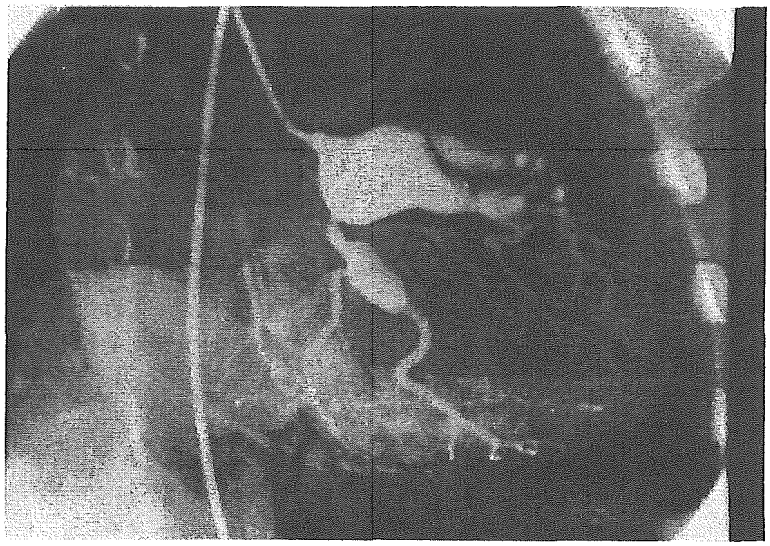

図１　川崎病に合併した冠動脈後遺症

使用された後の1996年12.1%，1999年6.2%，IVIG大量療法が行われている最近では5.9%と報告されている．死亡率は1974年までは１%以上であったが，1990年代は0.1%前後，2000年以後は0.05%である．

急性期の冠動脈炎からその後瘤形成に至るのは平均11.4病日に28.8%で，そのほかの例では30病日以後の回復期までには正常径にもどる．

最近はIVIG大量療法が用いられ，急性期瘤形成は18.1%[1]と減少している．しかし，臨床症状や炎症反応が早期に軽快した例でも，瘤を形成する時期はアスピリン単独療法同様12病日近辺が多い．さらに遅れて瘤を形成し，拡大し続ける例も稀にある．

最近では，CD40遺伝子多型と冠動脈障害発症リスクに相関があるとの報告がある[9]．

2．瘤の縮小・退縮と予後

冠動脈瘤の多くは回復期以後縮小傾向を示し，瘤が消失し造影上正常化する(退縮，regression)．発症から１～２年後に起こることが多い．冠動脈

表3　川崎病の心筋障害の種類

炎症性心疾患
心筋炎，心膜炎，心内膜炎
弁膜炎
刺激伝導系の炎症
虚血性心疾患
急性心筋梗塞，陳旧性心筋梗塞

障害例の32%[5]～50%[6]にみられている．病理学的な機序は内膜平滑筋細胞の内膜への遊走，増殖と血管内皮の再生である．小動脈瘤の退縮例でも成人した後に動脈硬化性病変の出現が認められており，臨床的にも若年性の動脈硬化症のriskが懸念される．中等瘤において発症後比較的早期に血栓により閉塞するものがみられる．局所性狭窄は，瘤の流入口部と流出口部の求心性の内膜肥厚によるもので，遠隔期にも活発な内膜肥厚が進行している．局所性狭窄は右冠動脈に比較し，左前下行枝近位部，主幹部に出現頻度が高い．血管内エコーでの検討では内径4 mmを越える瘤では内膜肥厚が認められる．

3．心筋障害[8]

病理学的な検討から，StageⅠ初期(第1～2週)，StageⅡ極期(第2～4週)，StageⅢ肉芽期(第4～7週)，StageⅣ陳旧期(7病週以後)の各stageに大きく分類される[1]．心筋障害の種類は大きく2つに分けられる．1つは急性期にみられる心筋炎や弁膜炎に伴う炎症性心筋障害であり，もう1つは冠状動脈炎に起因する冠動脈瘤と続発する虚血性心筋障害である(表3)．

急性期の治療[10]

治療のゴールは，“急性期の強い炎症反応を可能な限り早期に終息させ，結果として合併症である冠動脈瘤の発症頻度を最小限にすること”である．治療は第7病日以前に完全分子型IVIGが投与開始されることが望ましい．

表4　急性期川崎病へのIVIGの作用機序

リンパ球機能・増殖能の抑制
免疫グロブリン(自己抗体)産生能の抑制
単核球よりのサイトカイン，ケモカイン，接着因子の産生抑制とサイトカインアンタゴニスト産生促進
免疫複合体の溶出
リンパ球repertoiresの調整
FcR阻害
Super抗原の中和

1．IVIG単回大量療法

もっとも信頼できる抗炎症療法は，早期の大量(高用量)IVIG単回投与である．なかでも2 g/kg/日の超大量単回投与や，重症度に応じて1 g/kg/日を1日または2日連続して投与する方法がより効果的である．作用機序を表4にあげる．経口アスピリンは，抗炎症作用を期待する場合は30～50mg/kgの中等量で解熱するまで併用投与する．軽症例ではアスピリン療法単独でも効果を示すことが多い．しかし，抗血小板作用を期待するのであれば，aspirin paradoxを考慮しできる限り早期に3～5 mg/kgへの少量に減量すべきである．

2．IVIG不応例の治療選択[11]

IVIG療法開始後24～48時間においても不応例と判断された場合，いくつかの選択肢がある．効果の判定は通常24～48時間後までの解熱傾向や白血球数，好中球数，CRP値の低下で判断されている．15～25%程度に不応例が存在することが判明しているが，これらの不応例に対する治療法については，表5の選択肢があげられる．

表5　IVIG以外の治療[19]

治療法	投与方法	副作用と注意点
経口ステロイド (プレドニゾロン)	2 mg/kg/日　内服2週間 以後6週間かけて漸減中止	漸減時再燃あり 巨大動脈瘤とその破裂の頻度が高くなる危険性あり
ステロイドパルス (メチルプレドニゾロン)	30mg/kg/日 点滴静注 1～3日	高血圧，血栓症，電解質異常
好中球エラスターゼ阻害剤 (ウリナスタチン)	ミラクリッド®(持田)として 5,000単位/kg×3～6回/日 点滴静注　数日間	白血球減少，発疹
血漿交換 (5%アルブミン液)	循環血漿量と同じ 1～3日間	ショック，血管損傷

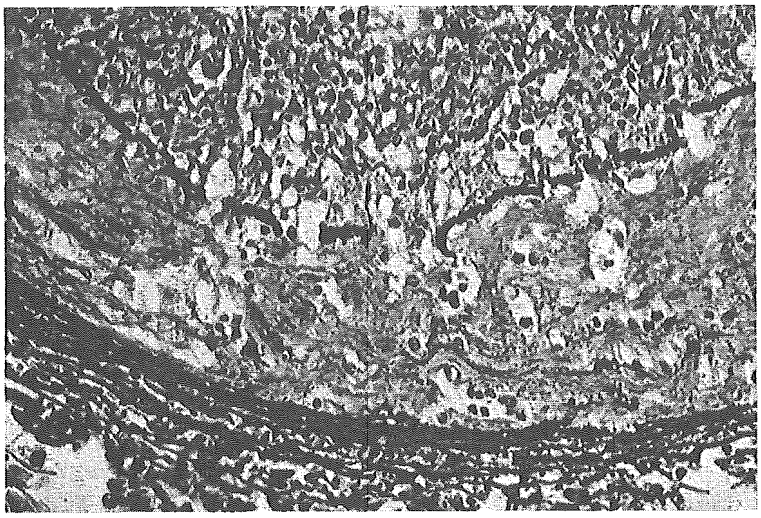

図2 冠状動脈炎の病理組織像
冠状動脈には内弾性板の断裂と全層性の炎症細胞浸潤が認められる．10病日死亡例(EvG染色)．

3. 抗血栓療法[8)]

死亡原因の多くは冠動脈瘤内で形成された血栓による血栓性閉塞と内膜肥厚による急性虚血性心疾患である．この血栓形成は，急性期に存在する内皮細胞障害や，血小板凝集能の亢進と著明な血小板数増加，血液凝固能亢進，冠動脈瘤内の血流停滞などが要因と考えられている．冠動脈障害を残さない場合でも，血小板凝集能は数か月間～1年間近く亢進しており，アスピリンは炎症の程度が陰性化した後2～3か月間は継続されるのが望ましい．

巨大冠動脈瘤を合併した場合にはアスピリン単独では血栓形成を防止できないことも知られており，チクロピジン，ジピリダモールなどほかの抗血小板薬や抗凝固薬(ワーファリン)の併用が望ましいとされている．閉塞性病変に対してはインターベンションによる治療法も対象となる[11)(注1)]．

〔注1〕冠動脈後遺症の管理については，『川崎病冠状動脈後遺症に対する治療に関するガイドライン』(厚生科学研究，班長：加藤裕久)，『川崎病心臓血管後遺症の診断と治療に関するガイドライン』(日本循環器学会，循環器病の診断と治療に関するガイドライン研究班，班長：原田研介)，『川崎病管理基準』(日本川崎病研究会運営委員会，2002年改訂)を参照．

剖検例からみたKD血管炎の特徴

KDは系統的血管炎症候群に属する疾患であり，全身の諸動脈，とくに中型の筋型動脈が好んで侵される．このうち，もっとも高頻度に侵襲されるのが冠状動脈であり，結果として生じる冠状動脈瘤の血栓性閉塞が生命予後に大きく関与する．

動脈瘤は左右冠状動脈の起始部や筋層外動脈分岐部に生じやすく，風船のように遠心性に拡張する球状あるいは紡錘状の単発性，多発性動脈瘤として認識される．瘤部分では渦流が生じるため血栓が形成されやすく，多くの急性期死亡例の冠状動脈瘤には内腔を閉塞する血栓が充満する．

病理組織学的に，冠状動脈病変のもっとも初期変化はKD発症後6～7日死亡例で観察される．冠状動脈の中膜平滑筋層が浮腫性に離開するものであり，中膜の水腫性疎開性変化と呼ばれている．炎症細胞浸潤は内膜および外膜に限局し，動脈壁全層に及ぶ炎症，すなわち汎血管炎は認められない．しかし，この直後に炎症は中膜に波及し，汎血管炎に至る[12)]．KD発症後10病日死亡例の冠状動脈には汎血管炎が生じていたが動脈瘤の形成はなかった．動脈壁には内膜，中膜，外膜に炎症細胞浸潤が観察され，内弾性板はところどころで断裂していた(図2)．免疫組織化学的手法を用い浸潤細胞の詳細を検索すると，主

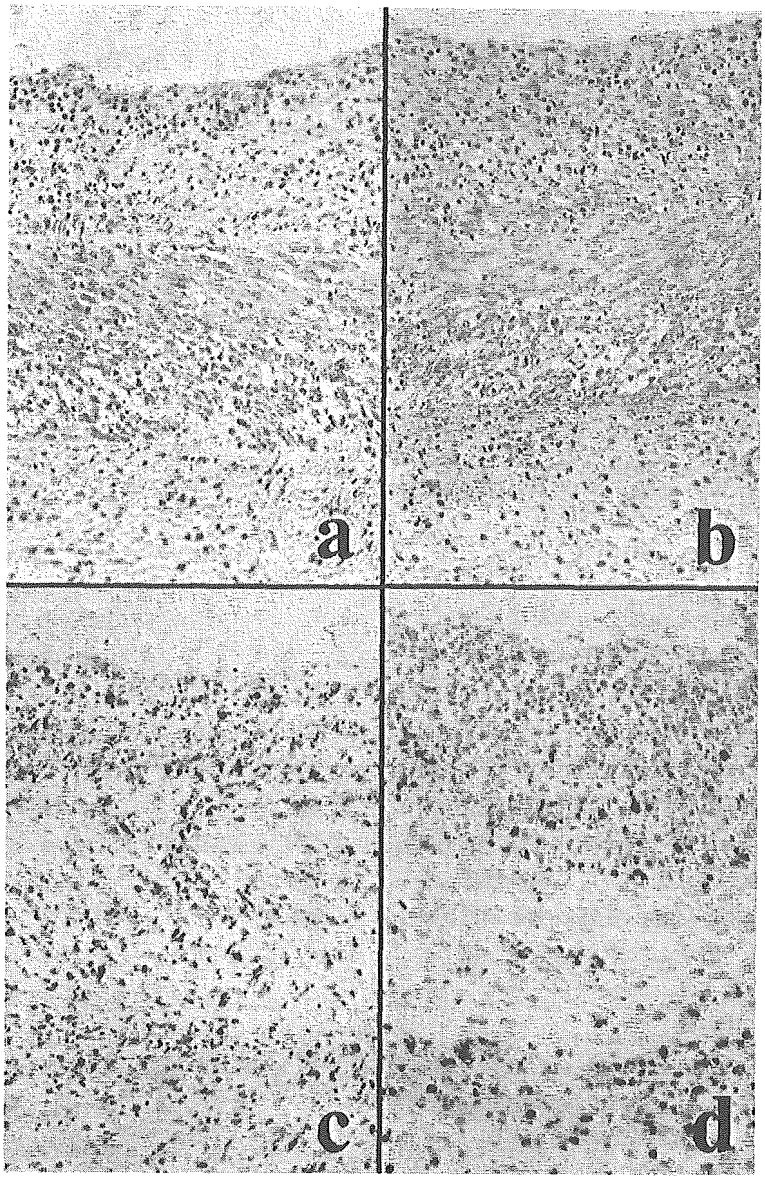

図3　免疫組織学的染色
a：smooth muscle actin, b：TypeⅣcollagen, c：CD68, d：neutrophil elastase.
血管壁の傷害とともに単球/マクロファージ，好中球の浸潤が認められる．10病日死亡例．

体はCD68陽性の単球/マクロファージで，T細胞やB細胞は内膜，外膜に少数分布していた．一方，中膜平滑筋細胞層にはCD68陽性細胞とともに好中球エラスターゼ抗体陽性の分葉白血球も観察された(図3)．この後，血管炎は動脈全周に広がり，動脈瘤は発症後10～12日で形成される．動脈瘤部には単球/マクロファージの著明な浸潤をみ，リンパ球や形質細胞が少数混在するが，好中球は大幅にその数を減ずる．動脈構築成分である中膜平滑筋細胞や内・外弾性板は確認できないほどになる(図4)．

このように，KD冠状動脈瘤は炎症のために動脈構築が著しく傷害されることにより生じるが，動脈構成要素のうち，とくに中膜平滑筋，内弾

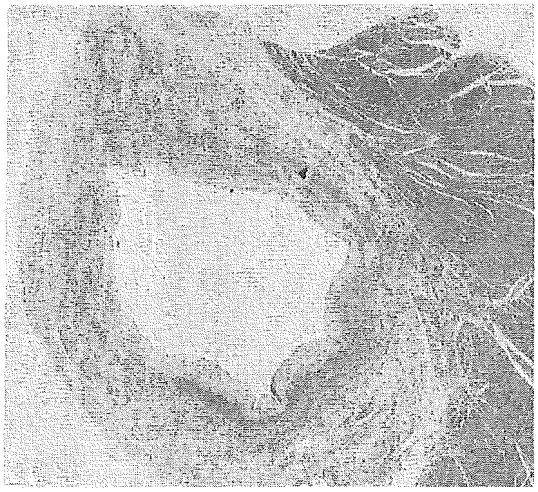

図4 冠状動脈瘤
23病日死亡例(HE染色)

性板が傷害されることが拡張への重要な因子となる[13][14]．これらが強く傷害された結果，内圧に抗しきれず動脈の拡張が始まる．一方，浸潤細胞からみた場合，KD動脈炎は単球/マクロファージの集積を特徴とする増殖性炎症であるが，動脈瘤形成に至る動脈構築破綻過程には好中球が強く関与していると推測される[15]．好中球から放出されるエラスターゼなどの蛋白融解酵素や活性酸素などが動脈を構成する諸細胞や細胞間マトリクスを傷害，破壊し，壁の脆弱化を招き動脈拡張が生じるのであろう．激しい炎症細胞浸潤は発症後25日頃まで継続した後，徐々に消退してゆく．そして血管炎の瘢痕が長期にわたり継続することとなる．

遠隔期病変の中で球状動脈瘤を残した場合，瘤壁に沿って層状あるいは顆粒状の石灰化がしばしば観察される(図5)．さらに，瘤の流入・流出部では新たな内膜肥厚の進展により内腔は狭窄に陥る．瘤内に複数の血管腔をみる血栓性閉塞後の再疎通血管も，新たな閉塞に陥るものが存在する．このような部位ではVEGFやPDGFなどの増殖因子が内皮細胞，内膜平滑筋細胞などで強く発現しており，遠隔期においても活発なremodelingが継続しているものと推測される[16]．

以上が，冠状動脈瘤形成に至るまでの組織学的推移および遠隔期変化の概略であるが，KD剖検例の中には肉眼的に動脈瘤を確認し得ない症例に遭遇することがある．急性期死亡例の場合には，動脈瘤に至る前段階で死に至ったと推測される病変に加え，動脈構築の完全破壊をきたさない程度の軽度の炎症にとどまっている病変が含まれる(図6)．一方，遠隔期例においては，急性期に炎症が存在したことを推定し得る血管炎の瘢痕を伴う動脈とともに，非KD小児対照例の冠状動脈と比較しても明確な差異を見出せない軽微な変化のみをみる症例が存在する．この

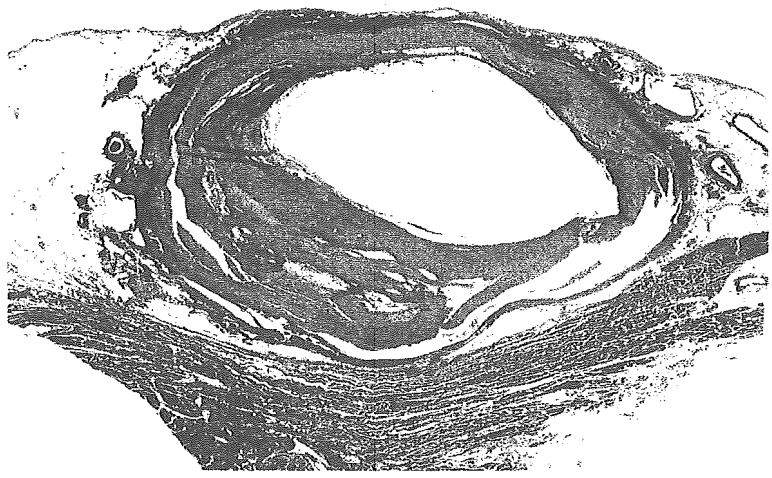

図5 冠状動脈瘤部の石灰化
瘤壁には全周性の層状石灰化を認める(青色で示した範囲)．発症後17年死亡例(HE染色)．

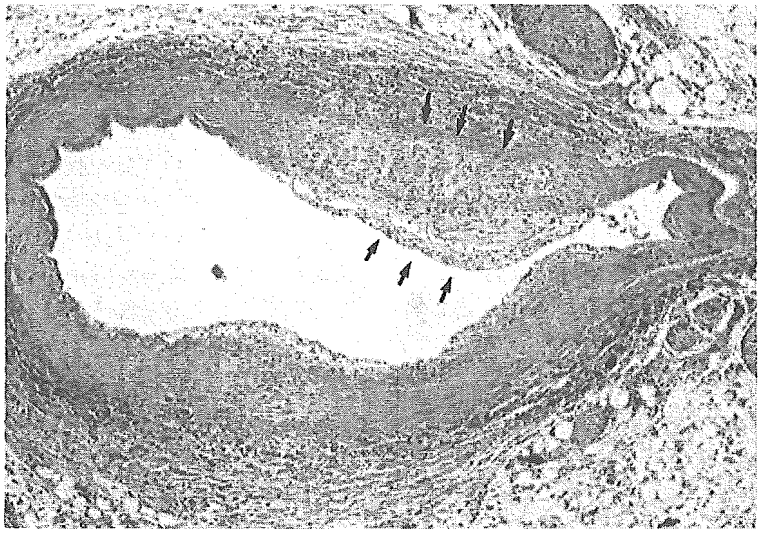

図6　瘤非形成性の冠状動脈
一部に軽度の炎症細胞浸潤を伴う内膜肥厚と弾性線維の断裂，中膜平滑筋層の乱れがみられる(矢印)が，動脈構築は基本的に保たれている．28病日死亡例(HE染色)．

ような瘤形成に至らない動脈変化に対して増殖因子について検索を加えたが，発症後1年以上を経過した後に死亡した症例では年齢を一致させた非KD症例の冠状動脈との間でPDGFやVEGFの発現分布，程度に差異を見出せなくなった[17]．KD罹患児の大部分は後遺症，つまり瘤を残すことなく治癒する．動脈瘤の形成をみなかった遠隔期剖検例の多くは一過性拡張や動脈瘤退縮例に相当すると推測されるものの，その一方で血管炎の痕跡を残さずに治癒する症例が存在することが示された．

動脈瘤を残した場合，遠隔期に新たな狭窄性病変が生じたり，粥状動脈硬化症の危険因子になり得ることは病理学的にも明らかにされている[18]．一方，動脈瘤を残さずに治癒するKD症例の長期予後についてはいまだ不明な点が多い．これまでのわれわれの検索結果ではこのような動脈に内膜肥厚が過度に進行して狭窄性病変へと進む危険性を示唆する知見は得ていないが，多くのKD罹患児の将来に関するきわめて重要な問題であり，今後，さらなる検討が必要である．

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