HISTOPATHOLOGICAL STUDY ON KAWASAKI DISEASE WITH SPECIAL REFERENCE TO THE RELATION BETWEEN THE MYOCARDIAL SEQUELAE AND REGIONAL WALL MOTION ABNORMALITIES OF THE LEFT VENTRICLE

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Thirty-eight consecutive patients with Kawasaki disease (18 patients with normal coronary artery and 20 with coronary artery lesions) were studied in order to find the incidence of myocardial abnormalities and the influence of the myocardial damage on the regional wall motion of the left ventricle in patients with Kawasaki disease with or without coronary artery lesion. Abnormal regional wall motion of the left ventricle was found in 28% of the patients with normal coronary artery (NCA) and in 55% of those with coronary artery lesions (CAL). Hypertrophy of myocytes, degeneration of myocytes and disarray were found frequently in the patients with CAL. The histopathology of endomyocardial biopsy taken from patients more than 3 years after disease onset and less than 3 years after onset were compared. Histopathologic abnormalities were found even in the biopsies taken more than 3 years after onset, especially from patients with coronary artery lesions, although the incidence of abnormalities was less frequent. We consider that repeat endomyocardial biopsies may be necessary in the patients who have significant histopathologic changes in the first endomyocardial biopsy to clarify the natural course of myocardial abnormalities, regardless of whether or not they have CAL.

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More than 100,000 cases of Kawasaki disease have been reported in Japan since the first report by Kawasaki in 1967. Despite worldwide interest and the large numbers of occurrences, etiology of Kawasaki disease remains unknown until now.

Because of the sudden cardiac death following myocardial infarction caused by coronary artery thrombosis, many studies focused on coronary artery lesions have been reported. However, it is well known that inflammation of other medium sized arteries, and of the myocardium, including specialized conduction tissue, also occurs. Abnormal regional wall motion is often observed in patients with ischemic heart disease. But there are few clinical reports regarding the relationship between the regional wall motion of the left ventricle and myocardial abnormalities detected by endomyocardial biopsy in patients with Kawasaki disease.

The purpose of this study is to investigate the incidence of myocardial abnormalities

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- Endomyocardial biopsy
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- Coronary artery lesion

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and the influence of the myocardial damage on the regional wall motion of the left ventricle in patients with Kawasaki disease with or without coronary artery lesions.

**PATIENTS AND METHODS**

**PATIENTS**

Thirty eight consecutive patients with Kawasaki disease, who were referred to Hirosaki University Hospital between April, 1985 and December, 1988, have been studied. Of these patients, 18 had normal coronary artery, they included 9 boys and 9 girls, aged 22 months to 19 years (mean: 5 years 9 months), and 20 patients had coronary artery lesions, [13 boys and 7 girls, aged 17 months to 14 years (mean: 4 years 11 months)]. Of the 20 patients with coronary artery lesions, 13 had coronary artery aneurysm, (9 boys and 4 girls) and 7 patients had coronary artery stenosis.

The diagnosis of Kawasaki disease was made according to the fourth revised diagnostic guideline of the Japan Kawasaki Disease Research Committee of the Japanese Ministry of Health and Welfare in 1984? Informed consent for cardiac catheterization was obtained from the parents of each child.

**METHOD**

The selective coronary arteriography was evaluated by the American Heart Association reporting system and coronary artery lesions was categorized as follows: coronary aneurysm is diagnosed when the aneurysmal dilation of coronary artery is more than 4 mm; and coronary stenosis is diagnosed when the reduction in luminal diameter of coronary artery is more than 25% by selective coronary arteriography. In this study all of the patients with coronary artery stenotic lesions had 25—75% coronary stenosis.

The method of calculation of the regional

![Diagram](image)

Fig.1. Calculating method of regional ejection fraction (REF) of the left ventricle. REF was calculated using the formula in the figure by computer.

![Graph](image)

Fig.2. Regional ejection fraction of the normally contracting left ventricle. Control value of regional ejection fraction (m±2sd) is shown in the figure.

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Fig. 3. Photomicrographs showing myocardial changes in endomyocardial biopsy specimens from patients with Kawasaki disease:
(a) moderate fibrosis and abnormal branching of myocardial fibers (Azan, ×200)
(b) disarray of myocardial fibers with slight fibrosis (hematoxylin-eosin, ×100)
(c) vacuolar degeneration (hematoxylin-eosin, ×100)
(d) slight interstitial cell infiltration and fibrosis (hematoxylin-eosin, ×200)

ejection fraction of the left ventricle for the evaluation of regional wall motion is shown in Fig. 1. The regional ejection fraction was calculated from the left ventriculography, the silhouette of which was divided into 49 regional areas by computer. The control values of regional ejection fraction in our Department are shown in Fig. 2. Regional wall motion abnormalities was diagnosed if three successive regional ejection fractions did not remain within the areas of 2 standard deviations.

The endomyocardial biopsy specimens were obtained from the septal aspect of the apex of the right ventricle using Machida’s biopsyte. Biopsy specimens were embedded in paraffin and stained with Hematoxylin-Eosin, Victoria blue-Van Gieson, Masson trichrome and periodic acid Shiff reaction. Histopathological findings was assessed for endocardial, interstitial changes, hypertrophy of myocytes, degeneration and disarray according to the diagnostic guidelines8,9 of the Sekiguchi and Pathological Subcommittee of Idiopathic Cardiomyopathy Research Committee of the Japanese Ministry of Health and Welfare. Inflammatory cell infiltration was recorded as positive10 when more than 5 inflammatory cells, either lymphocytes, plasma cells or polymorphonuclear leucocytes were present in one high-power field (×400).

Histopathologic comparison was made between the Kawasaki disease patients less than three years after onset (2 months to 2 years and 11 months) and those more than 3 years after onset (3 years to 14 years).

Typical histopathologic findings obtained from the patients with Kawasaki disease are illustrated in Fig. 3.

Statistic analysis of the incidence of each histopathologic finding in each group were performed using Fisher’s exact probability test, and p<0.05 was considered a significant difference.
RESULTS

1) Distribution of coronary artery lesions in 20 patients with Kawasaki disease

Bilateral coronary artery aneurysm was found in 8 out of 13 patients with coronary artery aneurysm. Coronary artery stenosis of the right coronary artery was found in 4 out of 7 patients with coronary artery stenosis.

2) Relation between regional wall motion abnormalities and coronary artery lesions in Kawasaki disease (Fig. 4).

Abnormal regional wall motion of the left ventricle was found in 28% of the patients with normal coronary artery and in 55% of the patients with coronary artery lesions.

3) Comparative incidence of histopathological abnormalities between Kawasaki disease with normal coronary artery and those with coronary artery lesions (Fig. 5).

Hypertrophy of myocytes, degeneration of myocytes and disarray were found more frequently in the patients with coronary artery lesion.

4) Comparative incidence of histopathological abnormalities in the patients with coronary artery aneurysm and those with stenosis (Fig. 6).

Hypertrophy, disarray and fibrosis were found more frequently in the patients with coronary artery stenosis.

5) Histopathological comparison between the patients less than three years after onset and those more than three years after onset in Kawasaki disease with normal coronary artery (Fig. 7).

All histologic features with the exception of fatty infiltrations were found more frequently when the biopsies were taken less than three years after disease onset.

6) Histopathological abnormalities in the pa-
tients with coronary artery lesions (Fig. 8).

Hypertrophy of myocytes, degeneration, interstitial fibrosis and endomyocardial changes were found more frequently in the biopsies taken more than three years after disease onset, than in those taken less than three years after onset.

**DISCUSSION**

Yutani and his colleague reported that histopathologic features of myocarditis was found in every biopsy case whether or not coronary artery lesions were demonstrated and the degree of abnormalities was correlated with the duration of the disease and they concluded that myocarditic lesion were universal feature and persisted in Kawasaki disease. There has been no report of pathologic evidence of myocarditis by endomyocardial biopsy in pediatric patients with Kawasaki disease during acute phase. However clinical and laboratory evidence of myocarditis has been reported to occur in about 50% of cases during the acute phase, most of which showed mild symptoms and signs of myocarditis and improved without any significant complications. Marcella et al. reported on the right ventricular endomyocardial biopsy findings and simultaneous ventricular function analysis of an adult with Kawasaki disease during the acute and recovery phase of the illness. They found marked pathologic features which were compatible with either viral myocarditis or an immunologically mediated form of myocarditis. In our series, the time interval between onset of disease and endomyocardial biopsy ranged from 2 months to 14 years and myocardial abnormalities could be detected in all time periods after disease onset. Although the incidence of abnormalities was much higher in the patients with coronary artery lesions, the degree of histopathology did not always correlated with the size and the extent of coronary artery involvement. According to serial endomyocardial biopsy

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studies, performed to analyze acute myocarditis of possible viral origin, findings at the convalescent stage (more than 4 weeks) revealed a near normal appearance, but significant findings were noticed in some cases of myocarditis by precise observation. Such histologic findings were categorized as post-myocarditic changes of myocytes, which was proposed by Sekiguchi. Those findings, such as hypertrophy of myocytes with deformed nuclei, abnormal branching of myocytes and increased interstitial fibrosis, were noticed in Kawasaki disease in patients with either coronary artery lesions or normal coronary artery, and there were remaining myocardial changes in the patients even after more than 3 years after onset of Kawasaki disease regardless of coronary artery lesions. According to Sekiguchi, such post-myocarditic changes were seen in some cases of dilated cardiomyopathy (DCM). From our endomyocardial biopsy findings histopathologic abnormalities of the myocardium appeared to persist, although clinical symp-

toms and signs of myocarditis disappeared in almost all patients with Kawasaki disease. Based on these findings we should be alert to the possibility of cardiomypathy developing in some cases of Kawasaki disease.

A high incidence of abnormal regional wall motion of the left ventricle was noticed in Kawasaki disease in patients with coronary artery lesions, but even some patients with normal coronary artery, had abnormalities. Factors affecting the regional wall motion included a previous myocardial infarction, regional ischemia due to stenosis, or obstruction of microvessels of the intramural coronary artery following angitis or myocarditis. Our biopsy specimens of Kawasaki disease included rare microvessels, which revealed mild changes in the tunica interna. As myocardial abnormalities were found in the patients without coronary artery lesions and the severity of coronary artery lesions did not always correlate with severity of histopathological abnormalities, it is probable that myocardial abnormalities in Kawasaki disease result from myocarditis. Myocardial ischemic changes due to intramural coronary artery stenosis or obstruction may in addition be related to the histopathological abnormalities of myocardium.

Anderson et al. evaluated sixty seven patients with Kawasaki disease using serial M-mode echocardiogram and concluded that patients with Kawasaki disease who did not have demonstrable coronary artery disease, exhibited abnormalities of cardiac chamber size and function long after their acute illness. Newburger et al. noticed early abnormalities of left ventricular contractility and myocardial performance and that improvement of such abnormalities was accelerated by administration of high-dose intravenous gammaglobulin in the acute phase of Kawasaki disease. As these reports did not include histopathologic investigation using endomyocardial biopsy, definite myocardial changes were unclear. It would be necessary to compare the functional state of the ventricle with histological features of myocardium. Our present study and the previous study by Yutani et al. found persistent late myocardial abnormalities but did not include children treated with intravenous gammaglobulin. The intravenous gammaglobulin effect on myocardial damage must be assessed by

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further investigation.
As the natural course of myocardial abnormalities of endomyocardial biopsy remains unknown and there have been few reports on myocardial changes using endomyocardial biopsy, repeat endomyocardial biopsy is desirable during the long-term follow-up in such cases with severe histopathological changes in the first endomyocardial biopsy regardless of coronary artery findings on the selective coronary arteriography, in order to evaluate residual myocardial damages.

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