ULTRASTRUCTURE OF THE MYOCARDIUM IN ACUTE FEBRILE MUCOCUTANEOUS LYMPH NODE SYNDROME

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A fine structure of the myocardium was examined in the acute febrile mucocutaneous lymph node syndrome, which was recently prevailing in Japan. The right ventricular myocardial cells in ten cases were observed through endomyocardial biopsies. On light microscopy, accumulation of histiocytes was demonstrated in some cases. Electron microscopic examinations revealed myofibrillar changes, increased glycogen contents and other degenerative changes. On the myocardium of a case in which a biopsy was performed during the active phase of the disease, these changes were prominent. However, these changes were also observed for some months to some degree.

SINCE Kawasaki's first description of 50 cases in 1967¹, infantile acute febrile mucocutaneous lymph node syndrome (MCLS) has been widely occurring all over Japan with increasing incidence. About seven thousand cases have been reported up to 1974 by the MCLS Research Committee. A high incidence of heart damage in MCLS has been recently noted^{2,3}. Electrocardiographic findings suggest that myocardial change may exist in more than ninety per cent of the cases⁴. One to two per cent fatalities of MCLS have occurred. The cause of the death was always myocardial infarction⁵ or rupture of the coronary aneurysm⁶ due to thromboarteritis of the coronary arteries, and the pathologic findings of fatal MCLS are indistinguishable from those of infantile polyarteritis nodosa⁷⁻⁹. However, the histological changes of the myocardium in a live case of MCLS are not yet known. The

purpose of this paper is to describe the histological changes of the myocardium in a live case of MCLS. Myocardial cells in MCLS were obtained through endomyocardial biopsy and were light and electron microscopically examined.

MATERIALS AND METHOD

For histological studies, right ventricular endomyocardial biopsy was performed on ten patients with MCLS. The specimens were obtained from the right ventricular outflow tract through endomyocardial biopsies according to Konno's technique¹⁰ at the time of the coronary angiography. Biopsies were performed at various intervals after the onset of the disease (Table I). The specimens were light and electron microscopically observed. For light microscopy, conventional stainings with hematoxylin eosin and with periodic acid-Schiff solution were carried out. For electron microscopy, the samples were fixed in cold 5% glutaraldehyde in phosphate buffer for 2 hours, washed in the same buffer for 24 hours, refixed in 1 per cent buffered osmium tetroxide for an hour, dehydrated by

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TABLE I CLINICAL DATA AND THE TIME OF BIOPSY AFTER THE ONSET OF MCLS

Name	1. N.H.	2. H.U.	3. T.H.	4. S.K.	5. S.H.	6. Y.I.	7. H.N.	8. K.N.	9. A.M.	10. N.S.
Age & Sex	5 F	1 M	5 M	5 M	1. M.	6 F	3 M	1 M	4 M	5 M
Duration of ESR over 30 mm	15 d	13 d	35 d	1 m	28 d	22 d	24 d	?	?	?
Maximum ESR & CRP	60/11+	61/7+	80/4+	38/6+	67/4+	62/5+	86/5+	?	?	?/6+
Treatment										
Beginning of treatment	5 d	3 d	30 d	7 d	10 d	—	15 d	?	?	?
Initial Dose of Prednisolone	1 mg/kg	2	2	2	2	—	2	?	?	?
Chest X-ray Maximum CTR	0.56	0.53	?	?	0.52	0.50	0.56	0.53	?	?
ECG Change										
PQ prolongation	—	—	—	—	+	—	—	—	?	—
QTc ≥ 0.44 sec.	+	—	+	—	—	—	+	+	?	—
ST (V5) ≤ -0.1 mV	+	+	+	+	—	—	—	—	?	+
T/R (V5) $\leq 1/6$	—	—	+	—	—	+	—	—	?	—
Biopsy	28 d	45 d	2.5 m	3 m	4 m	8 m	10 m	12 m	2 y	2.5 y

Fig.1. Accumulation of histiocytes (arrow) on the myocardium in MCLS. (Case 7) $\times 300$.

transfer through a series of acetone and embedded in epoxy resin. The sections were made with a Porter Wulm microtome, stained with uranyl

acetate and lead nitrate, and then examined under a Hitachi HU-11A electron microscope.

Fig.2. Myocardial cell shows intracellular edema and increased glycogen granules. (Case 1) $\times 12000$.

Fig.3. Markedly increased glycogen granules on the perinuclear area. (Case 1) $\times 7500$.

Fig.4. Glycogen granules are occasionally contained within membrane bounded structures. (Case 1) $\times 12000$.

RESULTS

Clinical course:

Clinical data at the acute phase and the time of biopsy on each case are described in Table I. All cases satisfied the diagnostic guideline of

Fig.5. Myocardiocyte in MCLS shows decreased myofibrils with loss of sarcomere structures and contraction bands. Increased lipid droplets and mitochondrial changes are also seen. (Case 4) $\times 8000$.

Fig.6. Myofibrillar degenerations with increased lysosomes in the affected myocardium. (Case 2) $\times 10000$

Fig.7. Myocardium shows large membrane bounded vesicles filled with amorphous granular materials. (Case 4) Disarrangement of myofibrils is also seen. $\times 8000$.

TABLE II LIGHT AND ELECTRON MICROSCOPIC FINDINGS IN MCLS

Name	1. N.H.	2. H.U.	3. T.H.	4. S.K.	5. S.H.	6. Y.I.	7. H.N.	8. K.N.	9. A.M.	10. N.S.
Biopsy	28 d	45 d	2.5 m	3 m	4 m	8 m	10 m	12 m	2 y	2.5 y
<i>Light Microscopy</i>										
cell infiltration	—	—	—	+	—	—	+	—	—	—
atrophic myocardium	—	—	—	+	—	—	—	—	—	—
edematous stroma	—	—	+	—	—	±	—	—	+	—
<i>Electron Microscopy</i>										
intracellular edema	+	—	—	—	—	—	—	—	—	—
membrane bounded vesicle	+	+	—	+	—	—	—	—	—	—
myofibrillar change	+	+	—	+	—	—	—	—	—	—
dilated S.R.	+	—	+	—	+	—	—	—	—	—
swelling of Mt.	+	+	—	+	—	—	—	—	—	—
glycogen granules ↑	+	—	—	+	+	—	+	—	+	—
lipid droplet ↑	+	+	—	+	—	—	+	—	—	—
lysosome ↑	—	+	+	—	+	—	±	—	—	+

S.R.: sarcoplasmic reticulum Mt.: mitochondria

MCLS and showed typical picture of MCLS.

In the first case, biopsy was performed during active phase of MCLS, while the others were biopsied at some intervals after the acute phase of the disease.

Almost all cases showed cardiomegaly to some degree. Electrocardiograms showed ST, T changes in 5 cases and other cases also showed some abnormal electrocardiograms. Coronary angiography was performed in all cases. The third and the seventh cases showed aneurysmal dilatation of main coronary arteries. The fourth and the tenth cases revealed normal coronary angiograms and 6 other cases showed narrowing of coronary arteries to some degree.

Light microscopy:

In the seventh case, mild edema was found in the myocardium. Accumulation of histiocytes was observed in the stroma and around the region, collagenous fiber was degenerated (Fig.1). In the fourth case, same inflammatory cells were occasionally seen. 8 other cases showed no significant changes except for slightly edematous stroma in some cases.

Periodic acid-Schiff reaction demonstrated increased glycogen contents of the myocardium in MCLS.

Electron microscopy:

Electron microscopic study of tissues biopsied from the apical portion of the right ventricular muscle revealed interesting abnormal findings in most patients. Such abnormal findings were remarkable in those patients on which biopsies were done at lesser intervals after the onset of the disease. No correlation could be established between the extent of the abnormalities and severity of the disease, abnormal findings on acute phase, or treatments.

The changes of the myocardium were relatively regional. In some areas, the myocardium appeared relatively normal whereas in other areas, the change appeared moderate to severe. The most prominent abnormality was observed in the case in which biopsy was done during the active phase of the disease. In this case, ventricular myocardial cells showed intracellular edema with markedly increased glycogen (Fig. 2). In the juxtanuclear sarcoplasm, dilated profiles of sarcoplasmic reticulum and excessive amounts of glycogen were seen (Fig. 3). The glycogen granules were for the most part dispersed in the sarcoplasm, but at times, were contained within

membrane bounded structure (Fig. 4). In some cases, myocardial cells showed loss of myofibrils with loss of sarcomere structures (Fig. 5, Fig. 6). The mitochondria were mostly normal, also sometimes smaller and denser, and showed occasional degenerative changes. A slight increase in lipid droplets and lysosomes were often observed. Myocardium sometimes contained large membrane bounded vesicles filled with some amorphous granular materials (Fig. 7).

Table II shows these light and electron microscopic changes in each case. On the myocardium of a case in which biopsy was performed during the active phase of the disease, these electron microscopic changes were prominent. However, even in a case in which biopsy was done 4 months after the onset of the disease, these changes were also observed to some degree. Increases in lipid droplets and lysosomes continued for several months.

DISCUSSION

Since MCLS was first established as a separate entity by Kawasaki¹ more than seven thousand cases were reported by 1974. The pathogenesis and etiology of this disease are not yet known, but, it was recently established that almost all cases of MCLS show cardiac abnormalities on electrocardiograms or chest roentgenograms^{4,11}. We have previously reported the relationship between clinical findings in the active stage of the disease and the pathologic change in the main coronary artery. In the present study, the histological change on the ultrastructure of muscle cells in MCLS was examined.

Cardiac involvement in MCLS may be divided into two groups, one resulting from myocardial ischemia due to coronary arteritis^{3,12} the other resulting from myocarditis and pericarditis^{13,14}. In our experience, ischemic type ST, T changes on electrocardiogram were more often observed in the cases which had coronary arterial changes on angiograms. These facts show that coronary arterial changes cause ischemic effects on myocardial cells.

These electron microscopic examinations on cardiac muscle cells showed that MCLS may induce quite same alterations on the affected myocardium. However, none of these changes encountered in MCLS are specifically related to this disease. Increased glycogen content in MCLS was also seen in some cardiomyopathies¹⁵. Increased numbers of degenerative organelles including lysosomes of variegated

morphology, autophagic vacuoles, lipofuscin pigment and lipid droplets were present in various degenerative conditions. These myocardial changes may not be due to direct invasion of causative agents, but, due to cell infiltration into the myocardium or ischemic changes from the pericarditis. The observations that the electron microscopic changes on the affected myocardium were regional, may show that these changes were due to ischemic changes from arteritis of the regional arterioles or small arteries.

In two cases, histological examinations of myocardium revealed a small focus of histiocytes which showed microinfarction. These changes may cause ischemic changes on the regional myocardium and may represent some degenerative changes in the affected myocardium.

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