DILATED CARDIOMYOPATHY IN A WISTAR RAT

Yoshimasa Okazaki, Junko Matsumoto, Osamu Katsuta, and Minoru Tsuchitani

Mitsubishi Chemical Safety Institute Ltd.

Abstract: A 57-week-old male Wistar rat died one week before the end of a toxicity study. Necropsy revealed subcutaneous edema, hydrothorax, dilatation of all cardiac chambers, and congestion in several organs. Light and electron microscopic examinations revealed myocardial hypertrophy, degeneration, fibrosis, and disruption of myofibrils and variable sized mitochondria. The entity is concluded to be dilated cardiomyopathy. (*J Toxicol Pathol* 8: 155~159, 1995)

Key words: Dilated cardiomyopathy, Myocardial hypertrophy, Disruption of myofibrils, Rat

Primary cardiomyopathy in humans is defined as heart muscle disease of unknown cause¹. Primary cardiomyopathy may be dilated, hypertrophic, or restrictive, of which dilated cardiomyopathy (DCM) is characterized by the dilatation of one or both ventricle or all four chambers as a result of cardiac failure. Dilatation often becomes severe and invariably accompanied by cardiac hypertrophy¹⁻⁴.

DCM has also been reported in dogs, cats, cattle, and hamsters^{3,5-9}. However, there is no report of true DCM in rats and mice.

The purpose of this communication is to describe the light and electron microscopic findings for DCM in a Wistar rat.

A 57-week-old, male Wistar rat, which had been employed in the medium-dose group in a 52-week repeated dose toxicity study of a test compound, died one week before the end of the treatment period. A complete necropsy was immediately performed. Histological examinations confirmed that the compound had had no toxic effects on the cardiovascular system.

For histological examinations, tissue specimens including cardiac specimens were fixed in

10% neutral buffered formalin, dehydrated in an automated processor, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (HE), Azan, periodic acid-Schiff (PAS), elastica Van-Gieson, and phosphotungstic acid-hematoxylin (PTAH). In addition, formalin-fixed cardiac tissues were examined by electron microscopy. The specimens were obtained immediately after death and were thus relatively well preserved.

Necropsy revealed severe subcutaneous edema extending from the head and neck to the thoracic area, and severe hydrothorax. The heart was severely enlarged. The sagittal sections of the heart presented obvious dilatation of the atria and ventricles (Fig. 1, inset), and both ventricular free walls were thin. The heart was discolored with white patches. A yellowish white nodule, 2 mm in diameter, was seen within the left ventricle.

Light microscopically, myocardial degeneration, myocytolysis, and interstitial or replacement fibrosis were noted in both ventricular free walls, the papillary muscles, apices, subendocardium of the interventricular septum, and both atria. Among these structures, the right ventricular free wall was most severely affected (Fig. 1). Most of the myocardial fibers were hypertrophic with enlarged nuclei, and their configuration was irregular (Fig. 2). Vacuolar degeneration, splitting (Fig. 3), and hyaline degeneration of myocardial fibers were also seen. Slight to moderate mononuclear

岡崎欣正 松本順子 勝田 修 土谷 稔

Accepted for publication: March 16, 1995

Mailing address: Yoshimasa Okazaki, Mitsubishi Chemical Safety Institute Ltd., 14 Sunayama, Hasaki-machi, Kashima-gun, Ibaraki 314-02, Japan.

Fig. 1. Severely affected right ventricular free wall. Myocardial degeneration and severe fibrosis are noted. Azan, $\times 110$. Inset: Sagittal section of the heart. Note dilated right atrium and both ventricles. HE, $\times 1.07$.

Fig. 2. Hypertrophied myocardial fibers and abnormal nuclei in the right atrium. Thickened endocardium is also seen. HE, $\times 330$.

cell infiltration was seen in the interstitium. Metaplastic osseous or cartilaginous tissue had formed in the papillary muscles and cordae tendineae (Fig. 4), and in the myocardium of the right atrium. The endocardium of both atria was thickened as a result of the proliferation of elastic fibers and collagen, but no thickening was detected in the endocardium of either ventricle. The nodule which was grossly visible in the left ventricle was an organizing mural thrombus with osseous metaplasia. Although slight intimal thickening was found in an intramural coronary artery, the surrounding myocardium was well preserved.

Congestion was found in the adrenals, kidneys, liver, and lung, atrophy in the thymus, and pyelitis in one kidney.

The most notable electron microscopic findings were disruption and loss of myofibrils. In these damaged myofibrils, dense accumulation of Z-band material was evident. The M and H bands recognized in normal myocardium were not distinguishable (Fig. 5). The irregularly shaped

Fig. 3. Severe fibrosis in the left ventricular free wall. Note splitting of myocardial fibers (arrows). Infiltrated mononuclear cells are seen in the interstitium. HE, $\times 180$.

Fig. 4. Cartilaginous metaplasia in the cordae tendineae. Myocardial degeneration, and interstitial and replacement fibrosis are noted. Hypertrophied myocardium (arrow) and mononuclear cell infiltration are also seen. HE, $\times 107$.

nuclei observed in most myocardial cells rarely presented invagination of the nuclear membrane. Mitochondria varied in size. In the atria, swollen mitochondria with loosely arranged cristae and distorted mitochondria were conspicuous (Fig. 6). Mild dilatation of the sarcoplasmic reticulum was occasionally seen.

Degenerative myocardial diseases including fibrosis are commonly seen in laboratory rats with no obvious clinical signs^{5,10,11}. There is a distinct age-related increase in incidence and severity, and the fibrosis is more extensive in older animals¹⁰. Therefore, the lesion has been designated chronic progressive cardiomyopathy (CPC). Although this condition is common in Fischer 344 and Wistar strain rats¹⁰, it is not usually seen in rats under 400 days of age⁵. The CPC lesion is distributed predominantly in the papillary muscles of the left ventricle and the left ventricular free wall^{5,11}. The age of the present rat was compatible with the age at which CPC is initially seen. However, this rat developed congestive heart failure, as manifested by the severe subcutaneous edema, hydrothorax, cardiomegaly, and congestion found mainly in the liver and lung. The distribution of the lesions in this rat differs from that in CPC. In addition, the myocardial degeneration, fibrosis, and nuclear pleomorphism in the present case were more severe than those in CPC.

All of the findings for the heart described

Fig. 5. Damaged myocardium in the left ventricular free wall. Disruption of myofibrils with dense accumulation of Z-band material is noted. The nuclear configuration is slightly irregular. N, nucleus. Bar = $2\ \mu\text{m}$.

Fig. 6. Damaged myocardium in the right atrium. Rupture of myofibrils is severe. Variable sized mitochondria are present, and, in swollen mitochondria, the cristae are loosely arranged. Mild dilatation of the sarcoplasmic reticulum is also seen. N, nucleus. Bar = 2 μ m.

above are among the pathological alterations which are observed in the heart in DCM^{1,2,7,12,13}. Therefore, these cardiac alterations seem to be similar to DCM rather than to CPC in rats.

In humans, significant coronary artery disease, vascular disease, systemic hypertension, and intracardiac shunt must be excluded to establish the diagnosis of cardiomyopathy^{3,14}. We noted minimal intimal thickening in one intramural coronary artery without significant damage to the surrounding myocardium, and no vascular lesion was found in other organs and tissues. Therefore, this intimal thickening is not considered to have been directly related to the cardiomyopathy.

In human DCM, four main pathologic pathways, which are alcohol toxicity, pregnancy-associated nutritional deficiency, genetic defect, and postviral myocarditis, are suspected^{2,14}. However, no conclusive evidence has been obtained. Some cases of canine and feline cardiomyopathy are caused by carnitine deficiency and taurine deficiency, respectively³. Cardiomyopathy in hamsters is a genetic disorder which is transmitted by an autosomal recessive gene⁶. In cattle as well, the possibility of genetic defect has been suggested⁹.

We could not verify the pathogenesis of the cardiac changes in the present rat. Consequently, this entity might be designated as dilated cardiomyopathy in a Wistar rat, as revealed by the necropsy, light and electron microscopic findings.

Acknowledgments : The authors are grateful to Ms. Yoshiko Hasegawa, Ms. Misako Ishige, and Mr. Takayoshi Itoh for excellent technical assistance.

References

1. WHO/ISFC Task Force: Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. *Br Heart J* 44: 672-673, 1980.
2. Roberts, WC, and Ferrans, VJ: Pathologic anatomy of the cardiomyopathies. Idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. *Hum Pathol* 6: 287-342, 1975.
3. Robinson, WF, and Maxie, MG: The cardiovascular system. In: *Pathology of domestic animals*, Vol 3, 4th ed, KVF Jubb, PC Kennedy, N Palmer Eds, pp. 1-48, Academic Press, San Diego, 1993.
4. Scotti, TM, and Hackel, DB: Heart. In: *Anderson's pathology*, 8th ed, LM Kissane Ed, pp. 560-662, The C.V. Mosby Company, St. Louis, 1985.
5. Ayers, KM, and Jones, SR: The cardiovascular system. In: *Pathology of laboratory animals*, Vol 1, K Benirschke, FM Garner, TC Jones Eds, pp. 1-69, Springer-Verlag, New York, 1978.
6. Liu, S-K, and Tilley, LP: Animal models of primary myocardial diseases. *Yale J Biol Med* 53: 191-211, 1980.
7. Sandusky Jr., GE, Capen, CC, and Kerr, KM: Histological and ultrastructural evaluation of cardiac lesions in idiopathic cardiomyopathy in dogs. *Can J Comp Med* 48: 81-86, 1984.
8. Van-Vleet, JF, and Ferrans, VJ: Myocardial diseases of animals. *Am J Pathol* 124: 98-178, 1986.
9. Watanabe, S, Akita, T, Itakura, C, and Goto, M: Evidence for a new lethal gene causing cardiomyopathy in Japanese black calves. *J Heredity*

- 70 : 255-258, 1979.
10. Lewis, DJ : Nonneoplastic lesions in the cardiovascular system. *In* : Pathobiology of the aging rat, Vol 1, U Mohr, DL Dungworth, CC Capen Eds, pp. 301-309, ILSI Press, Washington, D.C., 1992.
 11. MacKenzie, WF, and Alison, R : Heart. *In* : Pathology of the Fischer rat, GA Boorman, SL Eustis, MR Elwell Eds, pp. 461-472, Academic Press, San Diego, 1990.
 12. Roberts, WC : Cardiomyopathy and myocarditis : Morphologic features. *Adv Cardiol* 22 : 184-198, 1978.
 13. Van-Vleet, JF, Ferrans, VJ, and Weirich, KM : Pathologic alterations in congestive cardiomyopathy of dogs. *Am J Vet Res* 42 : 416-424, 1981.
 14. Cotran, RS, Kumar, V, and Robbins, SL : The heart. *In* : Robbins pathologic basis of disease, 4th ed, RS Cotran, V Kumar, SL Robbins Eds, pp. 597-656, W.B. Saunders Company, Philadelphia, 1989.