Nonspecific Myocarditis: A Statistical and Clinicopathological Study of Autopsy Cases

RYOZO OKADA, M.D., SACHIO KAWAI, M.D.
AND HIDEKI KASYUYA, M.D.

Among a total of 634,440 autopsy cases in "The Annuals of Pathological Autopsy Cases in Japan" from 1958 to 1984, 929 cases with nonspecific myocarditis were registered. The average incidence was 0.15%, fluctuating around 3- to 5-year intervals with a remarkable rise observed after 1974.

The major complications in cases of myocarditis were pneumonitis, hepatitis or hepatic cirrhosis, pancreatitis, malignancies, lymphatic or thymic involvements.

A clinicopathological study of 36 cases of myocarditis and 27 cases of postmyocarditic cardiomegaly indicated a classification of acute, subacute, healing and chronic or recurrent stages as well as dilatation- hypertrophy- and right ventricle-dominant types. Acute myocarditis was characterized by diffuse inflammatory cell infiltration and showed various types of arrhythmias and shock. Subacute myocarditis showed ventricular dilatation, edematous interstitium and severe congestive heart failure. Chronic myocarditis with dilatation and/or hypertrophy and irregular fibrosis included right ventricular involvement, endomyocardial disease, sick sinus syndrome in selected cases, congestive heart failure in most cases, and showed a male predominancy. Postmyocarditic cardiomegaly was similar to chronic myocarditis but showed more hypertrophy, preexcitation waves and prominent negative T waves in electrocardiography and sudden death.

WE previously reported the morphological problems of interstitial, idiopathic, viral and giant-cell myocarditis,¹ and a proposed rationale for including all myocarditis mentioned above as nonspecific myocarditis was stated. This paper presents the follow-up data on the nonspecific myocarditis from both autopsy statistics and clinicopathological comparisons.

Key words:

Nonspecific myocarditis
Autopsy statistics
Inflammatory cell infiltration
Myocardial fibrosis
Right ventricular myocarditis

MATERIALS AND METHODS

During the 27-year period from 1958 to 1984, 634,440 autopsy cases were recorded in The Annuals of the Pathological Autopsy Cases in Japan vol. 1-27.² The data included patients' age, sex, place of residence, clinical and pathologic diagnoses, a summary of the main pathologic findings and relevant therapy.

Cases with pathologic diagnoses of nonspecific, idiopathic, viral, interstitial and giant cell myocarditis were carefully selected. Specific types of myocarditis such as rheumatic, septic, mycotic, eosinophilic, and myocarditis associated with collagen disease, sarcoidosis, or other known

Research Laboratory for Cardiovascular Pathology, School of Medicine, Juntendo University, Tokyo, Japan

Meiling address: Ryozyo Okada, M.D., Research Laboratory for Cardiovascular Pathology, School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

Fig.1. Age and sex distribution of nonspecific myocarditis cases.

Fig.2. Yearly incidence of nonspecific myocarditis cases.

etiology were excluded from this study.

Among the autopsy cases collected in our laboratory, 36 cases of nonspecific myocarditis and 27 cases of postmyocarditic cardiomegaly were subjected to clinicopathological study. The cases of myocarditis included 8 in the acute, 2 in the subacute, 3 in the healing and 23 in the chronic stages. Postmyocarditic cardiomegaly (PMC) was defined as healed myocarditis with

dilatation and/or hypertrophy with a trace of inflammatory cell infiltrates and irregular patchy fibrosis rich in blood vessels.³⁻⁵

The autopsied hearts were examined by the authors macroscopically after formalin fixation. For routine microscopic examination, several tissue blocks, including the atria and ventricles, were taken. The tissue specimens were embedded in paraffin, thin sectioned at 7 microns in thick-

Fig.3. Yearly regional distribution of nonspecific myocarditis cases.

ness and stained with hematoxylin-eosin, elastic-van Gieson, azan and PAS methods. The conduction system was studied in 24 selected cases with arrhythmias according to Lev's serial sectioning methods^{6,7}

RESULTS

Nine hundred and twenty-nine cases with nonspecific myocarditis were found among the total 634,440 autopsy cases. The incidence was 0.15% and the male to female ratio was 520 : 409.

Figure 1 shows the age and sex distribution of the nonspecific myocarditis cases. The age at autopsy ranged from 3 days to 96 years. The distribution was widely scattered from young to old, slightly higher in the middle age range, and showed a two-peaked pattern in both sexes: one peak at less than 10 years and another in the 50- to 69-year range.

Of the total number of autopsy cases, there were 383,169 males and 246,951 females for a nonspecific myocarditis incidence of 0.14% in males and 0.17% in females.

Figure 2 shows the yearly incidence of non-

specific myocarditis cases. The annual incidence of the cases showed periodic fluctuations at 2- to 6-year intervals and an apparent increase after 1974. During the earlier half, from 1958 to 1971, the periodicities consisted of 4- and 5-year cycles. After no peak in 1972 the cycle length was shortened to 2- to 3-year intervals in the period to 1984.

Figure 3 shows the yearly regional distribution of nonspecific myocarditis cases. During the earlier half of the period, the propagation waves for nonspecific myocarditis started in the Kantō area both north and south with some echo phenomena, but after 1968, new waves started in the Chūbu area and showed interference with the waves from the Kantō area. In 1974, the number of cases with nonspecific myocarditis showed a synchronous peak in every area in Japan except the Kinki area.

Figure 4 shows the regional distribution of nonspecific myocarditis cases. The incidence was higher than average in the Chūbu and Kinki areas, less than average in Hokkaidō, Tōhoku, Shikoku and Kyūshū areas and approximately average in the Kantō and Chūgoku areas.

Table I lists the complications and treatments

Fig.4. Regional distribution of nonspecific myocarditis cases.

TABLE I COMPLICATIONS AND TREATMENTS OF NONSPECIFIC MYOCARDITIS CASES

Year	1958-1967	1968-1977	1978-1984
Duration	10 years	10 years	7 years
No. of myocarditis cases	66	344	473
Complication			
Pneumonitis	4 (6%)	33 (10%)	51 (11%)
Hepatitis	1 (2%)	25 (7%)	47 (10%)
Hepatic cirrhosis	1 (2%)	22 (6%)	25 (5%)
Pancreatitis	2 (3%)	16 (5%)	27 (6%)
Interstitial nephritis	1 (2%)	16 (5%)	16 (3%)
Meningitis/encephalitis	0	6 (2%)	21 (4%)
Lymphatic/thymic lesion	7 (11%)	30 (9%)	45 (10%)
Thyroiditis	1	7 (2%)	14 (3%)
Lymphoma/leukemia	1 (2%)	12 (3%)	13 (3%)
Malignancies	4 (6%)	33 (10%)	70 (15%)
Treatment			
Adrenocortical steroid	13 (20%)	67 (20%)	85 (18%)
Antineoplastic agent	3 (5%)	16 (5%)	38 (8%)
Irradiation	3 (5%)	9 (3%)	16 (3%)

of the cases with nonspecific myocarditis during the first 10 years, the middle 10 years and the last 7 years. Associated malignancies, pneumonitis, hepatitis, pancreatitis and meningitis and/or encephalitis increased with the course of time, but interstitial nephritis, lymphatic and/or thymic

involvement and thyroiditis were almost always complications.

The use of adrenocortical steroids and irradiation were almost equally observed during the 3 stages, but the use of antineoplastic agents increased only in the late stage.

Fig.5. Cell infiltration. Acute myocarditis in 62 year-old male. Hematoxylin-eosin stain, $\times 400$.

Fig.6. Interstitial edema. Subacute myocarditis in 23 year-old male. Hematoxylin-eosin stain, $\times 400$.

A clinicopathological comparison using 36 cases with nonspecific myocarditis and 26 cases with postmyocarditic cardiomegaly revealed the following results.

The acute myocarditis group consisted of 8 cases of which the male to female ratio was 4 : 4, the age range was from 1 month to 66 years with an average of 47 years, and the clinical course lasted 2 to 5 days with an average of 3 days. The electrocardiograms showed an elevation of the ST segment, atrioventricular block, right bundle branch block, abnormal QRS axis deviation, low voltage, abnormal Q wave, ventricular tachycardia and/or fibrillation. The mode of death was divided into cardiogenic shock in 5, sudden in 2 and congestive heart failure in 1 case. The average heart weight was 379g excluding the infant cases and the heart size was normal or mildly dilated. The histological abnormalities were interstitial inflammatory cell infiltration including lymphocytes, monocytes, plasma cells, eosinophil and/or scarce polymorphonuclear leukocytes with edema in the myocardium, and focal myocyte degeneration and necrosis as shown in Fig. 5. Multinucleated giant cell infiltration was observed in 1 case. The atrioventricular conduction system and Purkinje cells were also involved to a lesser or greater degree. Proliferation of the small vessels and fibroblast activity were also noticed. Each case of thymoma, thymic hypertrophy and dermatitis was complicated.

The subacute myocarditis group consisted of 2 cases: one male and one female, 23 and 77 years old, respectively, with a clinical course of 19 and 40 days, respectively. The electrocardiograms revealed a ST segment elevation, negative T wave, atrioventricular block, right

bundle branch block, abnormal Q and premature ventricular systole. The mode of death was congestive heart failure. The average heart weight was 385g and the heart was dilated in both cases, with more dilatation of the right ventricle than the left in one case. The histological examination of the myocardium revealed diffuse but irregular interstitial edema, inflammatory cell infiltration including lymphocytes, macrophages or histiocytes and plasma cells as well as fibroblasts, a proliferation of small vessels, focal myocyte degeneration and necrosis with calcium deposition, and segmentation or interruption of myocyte linings with a mild increase in fine collagenous fibers and adipose tissue, as shown in Fig. 6. The atrioventricular conduction system and Purkinje cells were also involved. Both were associated with rubella and pulmonary thromboembolism with endocardial thrombosis.

The healing myocarditis group included 3 cases; one male and two females, aged 2 to 15 years with an average of 10 years. The clinical course lasted 2 and 6 months in two of the cases, and was not known in 1 case. The electrocardiograms included a ST segment elevation, negative T wave, atrioventricular block, intraventricular conduction delay and ventricular fibrillation. The mode of death was sudden death in 2 cases and congestive heart failure in 1 case. The average heart weight excluding the infant case was 420g and the hearts were dilated without exception. The histological findings consisted of progressing fibrosis with irregular distribution, mild to moderate focal adiposis, endocardial fibroelastosis with organizing mural thrombosis, small number of lymphocytes, macrophages or histiocytes and plasma cells showing focal accu-

Fig.7. Fibrosis. Chronic myocarditis in 19 year-old male. Hematoxylin-eosin, $\times 40$.

Fig.8. AV bypass tract. Postmyocarditic cardiomegaly in 9 year-old male. Elastic-vanGieson's stain, $\times 13$.

mulation and abundant fibroblasts as well as fibrocytes. Fresh focal necrosis, degeneration, hypertrophy and derangement of myocytes were characteristically observed in this stage. The atrioventricular conduction system and Purkinje cells were also involved.

The chronic myocarditis group included 23 cases of which the male to female ratio was 15 : 8, the age range was from 1.5 to 80 years with an average of 50 years, and the clinical course lasted 8 months to 10 years with an average of 4 years but is not known in 2 cases. The electrocardiograms showed a left ventricular hypertrophy, ST and T wave changes, atrioventricular conduction disturbance, right or left bundle branch block, abnormal QRS axis, low voltage, abnormal Q wave, premature ventricular systole, atrial fibrillation, sick sinus syndrome and ventricular tachycardia and/or fibrillation. The mode of death was congestive heart failure in 18 cases, cardiogenic shock in 2 cases and sudden death in 3 cases. The average heart weight excluding the infant cases was 489g. The hearts were dilated in two thirds of the cases and hypertrophied in one third including 3 cases with hypertrophic cardiomyopathy-mimic shape, one case with discrete type subaortic stenosis, 4 cases with endomyocardial disease, 3 cases with extreme right ventricular dilatation, 1 case with extreme atriomegaly and 1 case with small ventricular septal defect. The histological features were scattered irregular fibrosis with rich vascularization, adiposis, endocardial fibroelastosis with mural thrombosis, low degree focal macrophages, lymphocytes and plasma cell infiltration, and decreasing activity of fibroblasts and fibrocytes as shown in Fig. 7. A small amount of giant

cell infiltration appeared in 5 cases. Myocyte hypertrophy with some degeneration and derangement was remarkable. The conduction system lesions consisted of fibrosis, adiposis and hypertrophy of the sinus node and its approaches, the atrioventricular node and its approach, the bundle of His, the bundle branches and Purkinje cells varying considerably in grades from case to case. Each case was complicated with mumps, measles, toxoplasma, parainfluenza infection, familial occurrence, alcohol abuse and hypereosinophilia.

The postmyocarditic cardiomegaly group included 26 cases; 16 males and 10 females. The age range was from 6 months to 80 years with an average of 38 years and the clinical course lasted 3 months to 26 years with an average of 5 years but is not known in 4 cases. The electrocardiograms showed a left ventricular hypertrophy, negative T wave, right or left bundle branch block, atrioventricular block, abnormal QRS axis deviation, abnormal Q wave, low voltage, non-specific ST-T change, sick sinus syndrome, pre-excitation wave (in 4 cases), premature ventricular systole, atrial fibrillation, and ventricular tachycardia and/or fibrillation. The mode of death was congestive heart failure in 21 cases and sudden death in 5 cases. The average heart weight excluding the infant cases was 555g. The hearts were dilated in three quarters of the cases and hypertrophied in one quarter including 5 cases with hypertrophic cardiomyopathy-mimic shape, 3 cases with endomyocardial disease, 2 cases with extreme right ventricular dilatation, 1 case with extreme atriomegaly and 1 case with atrial septal defect. The histological examination revealed widely scattered irregular fibrosis with

Fig.9. Calcium deposition and interruption. Subacute myocarditis in 23 year-old male. Azan stain, $\times 40$.

Fig.10. Derangement. Chronic myocarditis in 19 year-old male. Hematoxylin-eosin stain, $\times 40$.

partly rich vascularization, focal adiposis, endocardial fibroelastosis with organizing mural thrombosis. There was a scarce cell infiltration which could be found under careful search in several slices of the myocardial specimens. The presence of giant cells was observed in 1 case. Myocyte hypertrophy with mild degeneration was prominent with moderate derangement especially around the fibrotic foci. The conduction system was involved in a similar fashion to the chronic myocarditis group. In addition, multiple nodoventricular bypass tracts as shown in Fig. 8 and Mahaim's fibers in 3 cases as well as Kent's bundles in 1 case were observed using a serial sectioning method. Two cases showed familial occurrence, and each was complicated with seropositive Coxsackie B₂ or B₅ virus infection, measles, acromegaly, QT prolongation syndrome and Sjögren's syndrome.

In general, the pathologic lesions in the myocardium of the nonspecific myocarditis cases had a transition from diffuse to focal with a longer duration of the disease process. They were localized in one third of the cases in the subepicardial or subendocardial zone.

The monocytic infiltration which consisted mainly of lymphocytes, histiocytes or macrophages was observed in the interstitial and perivascular space with a small number of polymorphonuclear and eosinophilic leukocytes in the acute stage and increasing plasma cells and macrophages in the subacute stage. Fibroblast activity was seen even in the acute phase increasing in the subacute and healing stages and existed even in the chronic stage which is associated with monocyte infiltration. Necrosis and degeneration of the myocytes were usually associated with

interstitial inflammation in the acute stage but occasionally were observed independently in the subacute or healing stages and were of a focal and scattered nature.

Calcium deposition into the myocytes and interruption of the myocyte-linings were only seen in the subacute stage as shown in Fig. 9. The fibrosing process in the interstitium started at the subacute or healing stage and matured in the chronic stage with small but multiple progressing foci. The fibrosis turned to scar tissue in the postmyocarditic cardiomegaly cases generally with neither cellular activity nor progression.

The myocyte hypertrophy advanced from the healing stage to the chronic stage in the postmyocarditic cardiomegaly cases and the derangement of myocytes around the necrosis or fibrosis, as shown in Fig. 10, seemed to promote the hypertrophy.

Adiposis in the myocardium was usually associated with fibrosis and made focal accumulations of lipid-containing cells which started in the acute stage and advanced with time but became extraordinarily extensive like lipomatosis in selected cases with right ventricular dilatation in the chronic stage or postmyocarditic cardiomegaly cases as shown in Fig. 11. Fibrosis, adiposis and the loss of myocytes were especially noticeable in the dilated thin wall of the right atrium in the peculiar atriomegaly cases of the chronic stage or postmyocarditic cardiomegaly.

The sinus node showed increased fibrosis in many cases with chronic myocarditis or postmyocarditic cardiomegaly and it was especially marked in cases with sick sinus syndrome as shown in Fig. 12. Adiposis and fibrosis at the approaches to the sinus node were also noted in

Fig.11. Right ventricular lipomatosis with endocardial fibroelastosis. Chronic myocarditis in 28 year-old female. Endocardium is from the right side. Elastica-VanGieson's stain, $\times 13$.

cases with atrial arrhythmias.

Interruptions of the bundle of His, the right or left bundle branches and the net of Purkinje cells due to active inflammation, fibrosis and or adiposis were observed in many cases corresponding to electrocardiographic changes. The existence of the atrioventricular bypass tracts was limited to cases with postmyocarditic cardiomegaly. It was associated with hypertrophy and derangement of both conducting and working myocytes around the AV bypass tracts.

DISCUSSION

The incidence of 0.15% for nonspecific myocarditis in our study is less than the 0.35% for isolated myocarditis in medicolegal cases.⁸ Our materials were limited to autopsy cases in the departments or institutes of pathology attached to middle to large hospitals in Japan and, therefore, they did not include a majority of sudden death cases outside hospitals. The difference suggests the existence of a considerable number of unexplained or sudden deaths in myocarditis.

The yearly fluctuation of the incidence of nonspecific myocarditis suggests an infectious origin of this disease either with the propagation being influenced by the immunity of the population or with a periodical mutation or alteration of the pathogenic microorganisms. Its lower incidence in the islets separated from the mainland (Honshū) by the straits also advocates its infectious origin.

The recent increase in myocarditis incidence is partly explained by an increase in opportunistic infections in compromised hosts such as cases

Fig.12. Sinus node fibrosis. Postmyocarditic cardiomegaly in 80 year-old male. Sinus node is on the right side. Elastica-van Gieson's stain, $\times 13$.

with malignancies being treated with potent antineoplastic drugs which are known to reduce the immunocapacity provoking secondary viral infections.⁹ The short irregular periodicities of the myocarditis incidence after 1972 seemed to depend on the existence of double center propagation waves: one from the Kantō area and the other from the Chūbu area.

It has been generally accepted that myocarditis is etiologically related to cardiomyopathies but the ratio of participation of the former to the latter condition is still controversial.^{3-5,10} We found 27 cases of postmyocarditic cardiomegaly which were presumptively accepted as cardiomyopathies as well as 36 cases of myocarditis during the same period and the ratio of the former to the latter was 1 : 1.3. The ratio of autopsy incidence of cardiomyopathies to nonspecific myocarditis was 2.6 : 1 in The Annuals of the Pathological Autopsy Cases in Japan.² Therefore, 30% of cardiomyopathies seem to be etiologically related to myocarditis from our data. This 30% ratio is strikingly matched to the 31% incidence of postmyocarditic cardiomegaly in cardiomyopathies in our previous report.⁵

From our clinicopathological study of nonspecific myocarditis, the classification of acute, subacute, healing and chronic stages seems to be rational. The male to female ratio of our materials shows a male preponderance only in chronic myocarditis and postmyocarditic cardiomegaly. This suggests the existence of a factor that

interferes with the proper healing process of myocarditis in males.

Increasing heart weights with prolonged periods of myocarditis indicate a progression of a compensatory hypertrophy of the surviving myocytes. The evidence that the major group of myocarditis and postmyocarditic cardiomegaly shows dilated cardiomyopathy-mimic dilatation-predominant hypertrophy suggests an insufficiency of the compensatory hypertrophy in many myocarditis cases. Minor groups consisting of the hypertrophic cardiomyopathy-mimic type, endomyocardial disease type, right ventricular dilatation type and atriomegaly type include some interesting cases.

The inflammatory process in the myocardium could cause an increase in catecholamine release as well as abnormal immune reactions. Myocyte injuries by both pathogenic microorganisms and catecholamine or other reactive products resulted in compensatory hypertrophy in the period of repair to an adequate level for some cases or to an inadequate level for the other cases. When the myocyte injury turns to fibrosis or adiposis, which make many interruptions of the myocyte-linings including the conduction system cells, various fatal accompanying arrhythmias could occur.¹¹⁻¹³ Some of the injuries in the conduction system have a possibility of secondary involvement during the repairing or hypertrophying processes through rich nerve endings which could be hyperactive during or after the inflammation.¹¹⁻¹³ The high incidence of atrioventricular bypass tracts in postmyocarditic cardiomegaly cases suggests the possibility either of hypertrophy of preexisting accessory pathways or of newly formed pathways during the repair process after the inflammatory destruction.¹⁴ The increase of adipose tissue or lipomatosis of the myocardium associated with chronic inflammation could make right ventricular dysplasia-mimic features which are sometimes arrhythmogenic.¹⁵ The reason why the right side of the heart is selectively involved in some cases is still unknown, but some differences in the sites of viral invasion which involves the autonomic nerve system controlling the heart and results in myocyte injury through a cardiotoxic substance which is released from nerve endings, may cause a peculiar deviation of the adiposis or fibrosis distribution.

The majority of cases in this series are thought

to be of viral origin from histological findings, but only a few cases could be identified as being caused by a specific viral infection. This study was supported partly by a grant for group study of cardiomyopathies from the Ministry of Health and Welfare of Japan.

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