

# Two Cases of Persistent Myocarditis Developing into Dilated Cardiomyopathy

Jaime Koiti TSUKIMATA<sup>1</sup>, Makoto KODAMA<sup>1</sup>, Satoru HIRONO<sup>1</sup>, Makihiko SAEKI<sup>1</sup>, Kiminori KATO<sup>1</sup>, Haruo HANAWA<sup>1</sup>, Tohru IZUMI<sup>1</sup>, Akira SHIBATA<sup>1</sup>, Kaoru SUZUKI<sup>2</sup>, Shigeo KIDO<sup>2</sup> and Makoto KUMAKURA<sup>2</sup>

<sup>1</sup>The First Department of Internal Medicine, Niigata University School of Medicine, Niigata, <sup>2</sup>Niigata Prefectural Shibata Hospital, Shibata, Japan

Received January 17 1995; accepted April 11 1995

**Summary.** The clinical course of the progression of myocarditis into dilated cardiomyopathy is not precisely understood. We observed two cases of acute-onset and persistent myocarditis in which the left ventricle developed into a dilated and poorly contracting state even after the healing of the myocarditis. Neither case had symptoms of previous infection. Similar characteristics of the two cases included a fulminant clinical course during the acute phase involving broad anterior myocardial damage, the persistence of myocardial inflammation over two months, and the resolution of myocardial inflammation by pulse therapy with methyl-prednisolone. The severity of myocardial damage during the acute phase and the persistence of myocarditis were considered responsible for the progression of myocarditis into post-myocarditis dilated cardiomyopathy. Pulse therapy using methyl-prednisolone appears useful in some patients with myocarditis which develops into dilated cardiomyopathy.

**Key words**—acute myocarditis, persistent myocarditis, dilated cardiomyopathy, endomyocardial biopsy, steroid therapy.

## INTRODUCTION

Dilated cardiomyopathy is characterized by left ventricular dysfunction and by the progressive development of heart failure. Chronic myocardial damage caused by various etiologies is considered to be responsible for the development of dilated cardiomyopathy.<sup>1,2)</sup> One of the possible causes of dilated cardiomyopathy is a sequel of myocarditis.<sup>3,4)</sup> Myo-

carditis causes congestive heart failure and left ventricular dysfunction during the acute phase, but both symptoms improve in accordance with the recovery of myocarditis.<sup>5,6)</sup> For this reason, other factors that cause progressive myocardial damage are believed to underlie the pathogenesis of post-myocarditis dilated cardiomyopathy, such as a persistent viral infection,<sup>7-9)</sup> an inappropriate defensive response of the immune system,<sup>10-12)</sup> or progressive autoimmune myocardial damage.<sup>13-15)</sup> Observation of the clinical course of patients with myocarditis developing into dilated cardiomyopathy may reveal the pathogenesis of post-myocarditis dilated cardiomyopathy. However, the total clinical course of patients with acute myocarditis developing into dilated cardiomyopathy has rarely been fully described. We encountered two cases of acute myocarditis in which post-myocarditis dilated cardiomyopathy developed after persistent inflammation of the heart.

## CASE REPORTS

### Case 1

A 54-year-old man enjoyed good health until August 29, 1993, when he developed a fever. Two days later, he developed dyspnea on exertion. On the following day, the patient went into shock and entered another hospital. The electrocardiogram revealed a sinus tachycardia of 153/min, and an abnormal Q wave with ST elevation in leads V1 to V6. The chest radiogram showed cardiomegaly and mild pulmonary congestion. The cardio-thoracic ratio was 58%. An echocardiography demonstrated a poorly contracting left ventricle. The left ventricular end-diastolic dimension was 4.9 cm and the fractional shortening

Correspondence: Jaime Koiti Tsukimata, M.D., The First Department of Internal Medicine, Niigata University School of Medicine, 1-754 Asahimachi, Niigata 951, Japan.

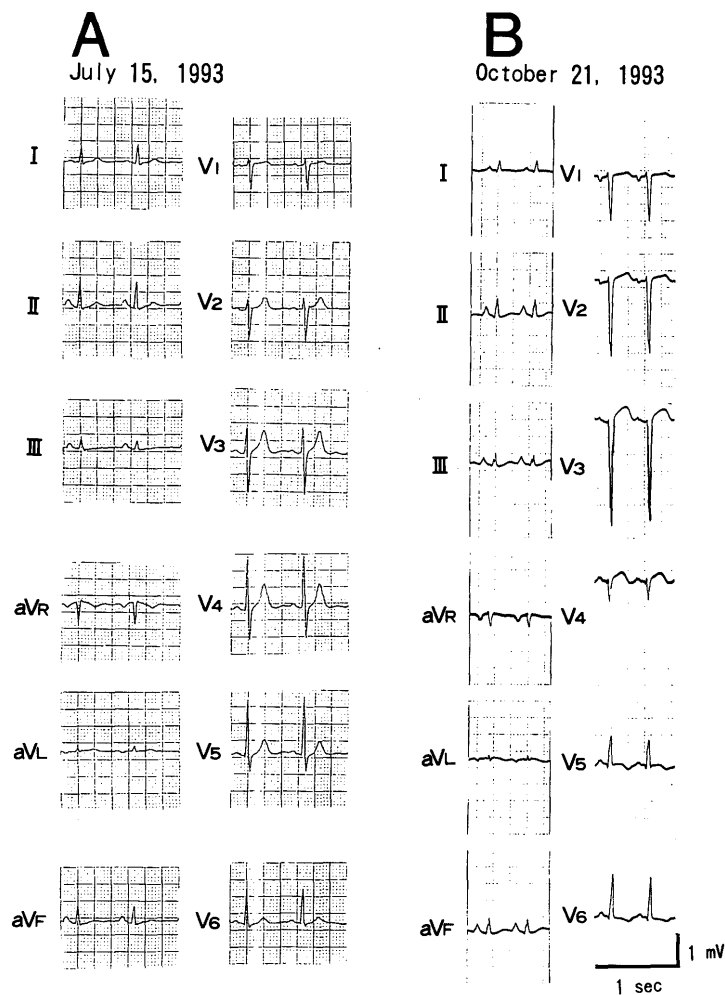
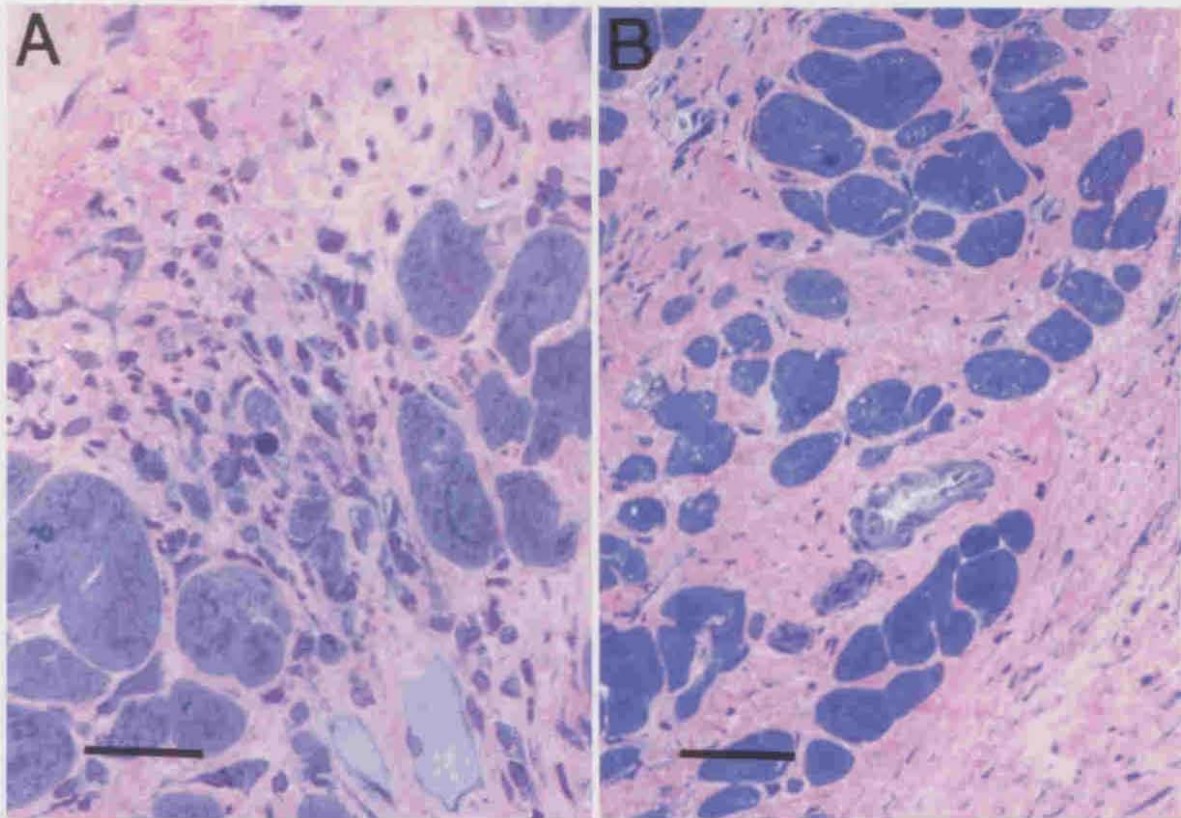


Fig. 1. Electrocardiograms of Case 1. Left **A** was taken before the onset of myocarditis and right **B** was taken at admission into our hospital.

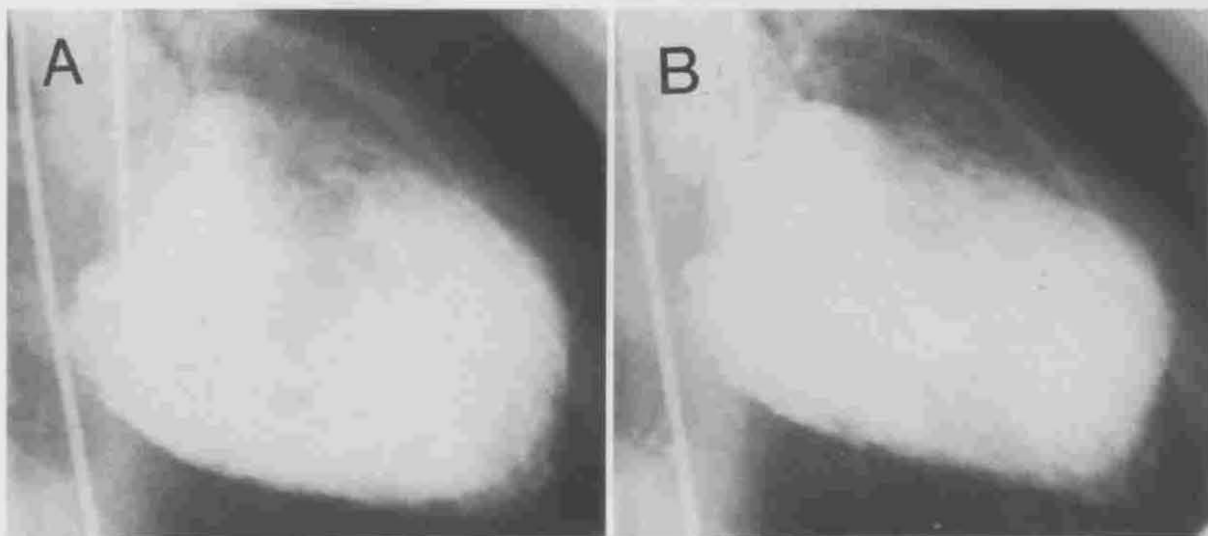
was 20%. Coronary arteriography revealed no significant stenosis. Hemodynamics of the patient were supported using an intra-aortic balloon pumping system for two weeks.

The patient was transferred to our hospital due to intractable heart failure continuing for more than two months. Blood pressure was 88/52 mmHg, the heart rate was 125/min, and the rhythm was regular. A third heart sound was heard. No rales were heard over either lung. The abdomen was normal. Slight pretibial edema was detected. A neurological examination disclosed no focal abnormalities. Abnormal laboratory data were as follows: GOT 33 IU/L, GPT 41 IU/L and LDH 893 IU/L. An electrocardiogram showed sinus tachycardia and abnormal Q wave in leads V1 to V5 (Fig. 1). An echocardiography showed diffuse hypokinesia of the left ventricle. The left

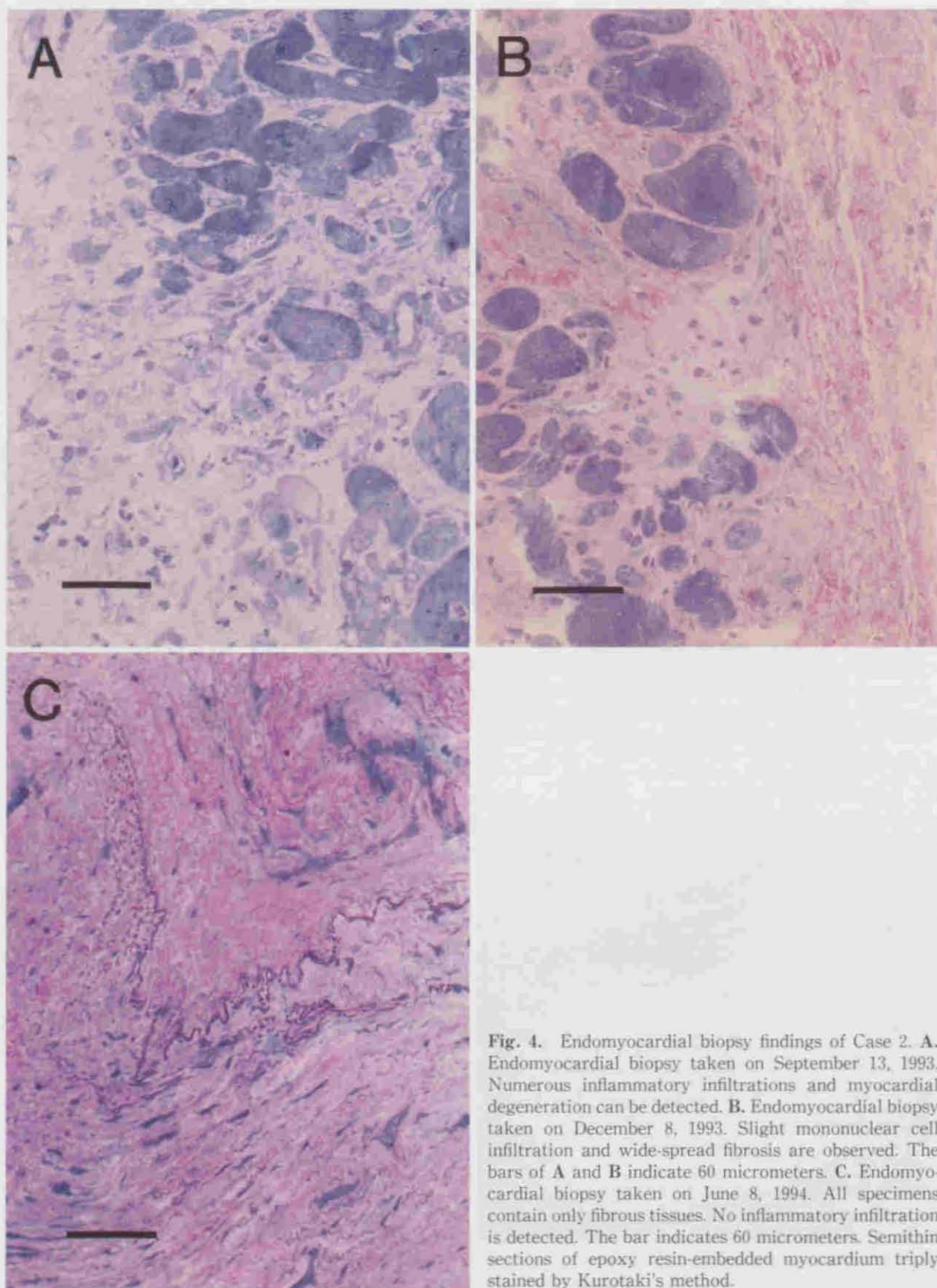
ventricular end-diastolic dimension was 6.5 cm and the fractional shortening was 9%. The endomyocardial biopsy specimens from the left ventricle revealed active myocarditis (Fig. 2A). Because there was still evidence of myocarditis, we decided to give steroid pulse therapy to the patient, in order to halt the inflammation and therefore avoid further progression of left ventricular dysfunction. We gave the patient 1,000 mg of methyl-prednisolone for three days. After steroid therapy, the sinus rate decreased and the third heart sound became inaudible. Congestive heart failure did not worsen even after the cessation of dobutamine and dopamine. One month after steroid therapy, the patient again underwent cardiac catheterization. Endomyocardial biopsy revealed healed myocarditis (Fig. 2B). Although active myocarditis had been healed, a left ventriculography revealed the



**Fig. 2.** Endomyocardial biopsy findings of Case 1. **A.** Endomyocardial biopsy taken on November 10, 1993. Marked mononuclear cell infiltration and myocardial degeneration can be observed. The bar indicates 30 micrometers. **B.** Endomyocardial biopsy taken on January 5, 1994. Inflammatory infiltrations have disappeared and widespread fibrosis is observed. The bar indicates 60 micrometers. Semithin sections of epoxy-embedded myocardium were triply stained by Kurotaki's method.



**Fig. 3.** Left ventriculography of Case 1 on January 5, 1994. Left **A** shows end-diastole and right **B** shows end-systole. A dilated and poorly contracting left ventricle is observed.



**Fig. 4.** Endomyocardial biopsy findings of Case 2. **A.** Endomyocardial biopsy taken on September 13, 1993. Numerous inflammatory infiltrations and myocardial degeneration can be detected. **B.** Endomyocardial biopsy taken on December 8, 1993. Slight mononuclear cell infiltration and wide-spread fibrosis are observed. The bars of **A** and **B** indicate 60 micrometers. **C.** Endomyocardial biopsy taken on June 8, 1994. All specimens contain only fibrous tissues. No inflammatory infiltration is detected. The bar indicates 60 micrometers. Semithin sections of epoxy resin-embedded myocardium triply stained by Kurotaki's method.

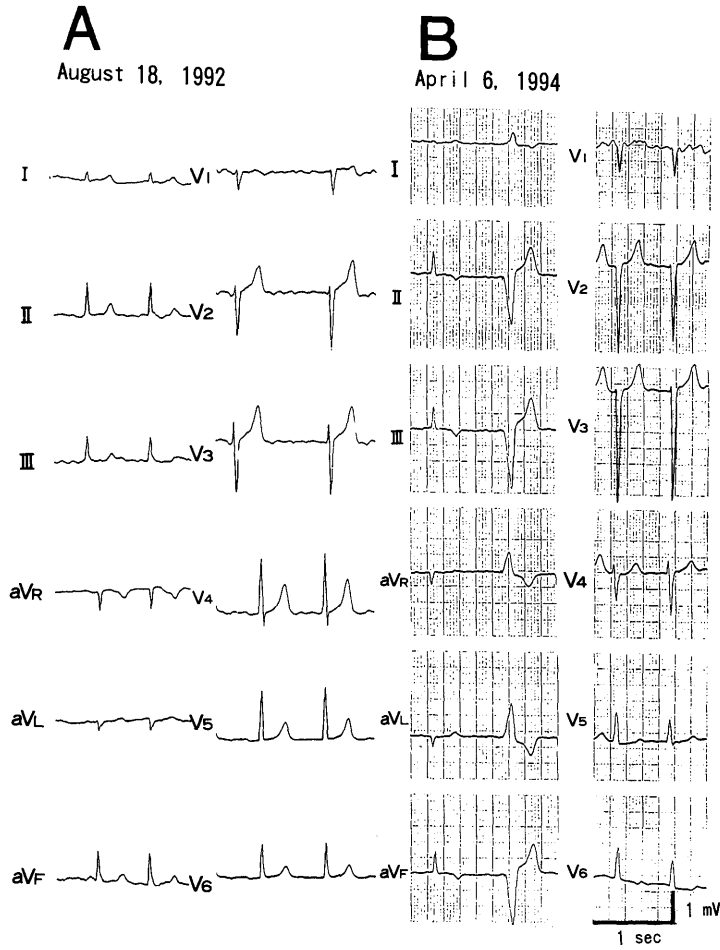


Fig. 5. Electrocardiogram of Case 2. Left A was taken before the onset of myocarditis and right B was taken at admission into our hospital.

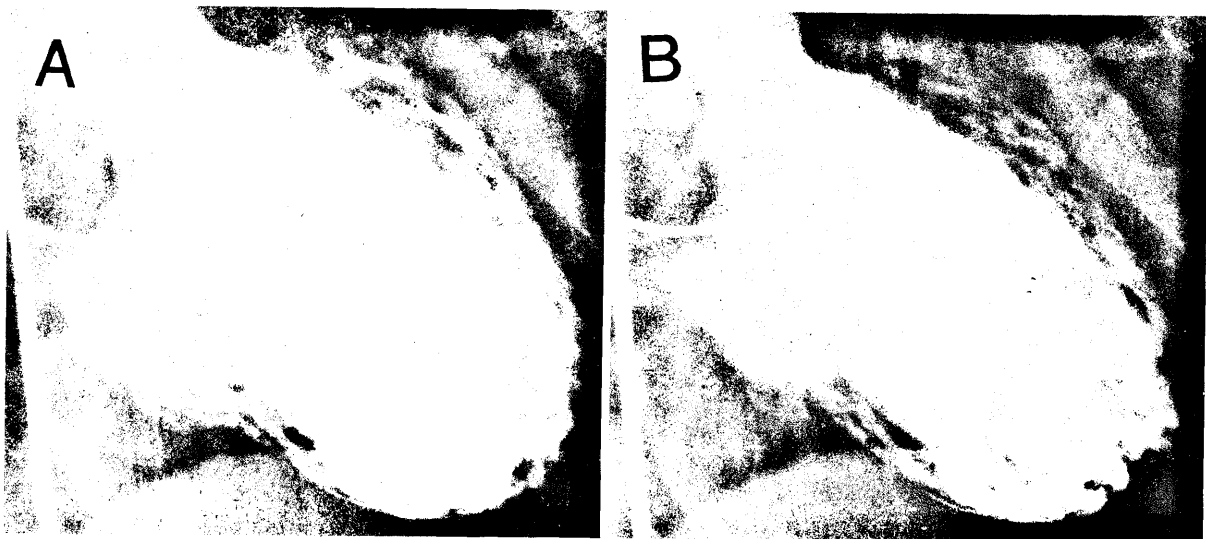


Fig. 6. Left ventriculography of Case 2 on June 8, 1994. Left A shows end-diastole and right B shows end-systole. A dilated and poorly contracting left ventricle is observed.

persistence of the dilated and poorly contracting left ventricle (Fig. 3).

## Case 2

A 63-year-old man developed fever and dyspnea on August 22, 1993. Five days later, he entered another hospital because dyspnea worsened. Echocardiographic examination demonstrated diffuse hypokinesia of the left ventricle and a severe mitral regurgitation. Abnormal laboratory data were as follows: CK 511 IU/L, CK-MB 40 IU/L, BUN 43.4 mg/dL, GOT 707 IU/L, GPT 702 IU/L. A high degree atrio-ventricular block was detected in his electrocardiogram and a temporary pacing catheter was inserted. His hemodynamics were supported using dobutamine. On September 13, the patient underwent cardiac catheterization. Coronary arteriography did not show any significant stenosis. Left ventriculography demonstrated a severely reduced left ventricular wall motion and the ejection fraction was 31%. The finding of an endomyocardial biopsy was active myocarditis (Fig. 4A). On December 8, he underwent a second catheterization. Left ventriculography showed a severely reduced wall motion, and the ejection fraction was 25%. The finding of an endomyocardial biopsy was persistent myocarditis (Fig. 4B). He was discharged from the hospital because of clinical improvement, in spite of the persistence of myocarditis. On March 30, 1994, he again developed dyspnea and entered the hospital.

On April 6, the patient was admitted to our hospital because of recurrent congestive heart failure and the persistence of myocarditis. On physical examination, blood pressure was 90/60 mmHg and the heart rhythm was irregular. No rales were heard over either lung. Abdomen and neurological examination were normal. Pretibial edema was not detected. Abnormal laboratory data were as follows: BUN 36 mg/dL, Creatinine 1.1 mg/dL and LDH 435 IU/L. An electrocardiogram showed atrial fibrillation and frequent ventricular pacing beats. Poor R wave progression was present in leads V1 to V3 (Fig. 5). The chest radiogram showed cardiomegaly and the cardiothoracic ratio was 55%. An echocardiographic examination showed diffuse hypokinesia of the left ventricle. The left ventricular end-diastolic dimension was 6.4 cm and the fractional shortening was 17%. Because the inflammation was still evident, we decided to give the patient steroid pulse therapy, in order to avoid further progression of left ventricular dysfunction. We gave the patient 1,000 mg of methylprednisolone for three days. After steroid therapy, the patient presented symptomatic improvement. On

June 8, he again underwent cardiac catheterization. Left ventricular wall motion was still diffusely reduced. The left ventricular end-systolic volume index was 116 ml/m<sup>2</sup> and the ejection fraction was 25% (Fig. 6). The finding of endomyocardial biopsy was healed myocarditis (Fig. 4C). In spite of the histologic evidence of the resolution of myocarditis, no significant improvements were detected in the global left ventricular function or wall motion.

## DISCUSSION

The total clinical course of the progression of acute myocarditis into post-myocarditis dilated cardiomyopathy as described here, had similar clinical characteristics, such as: 1) acute onset without preceding infection; 2) a severe and fulminant course during the acute phase; 3) the involvement of broad anterior myocardial damage demonstrated by an electrocardiogram; 4) the persistence of myocardial inflammation for over two months; and 5) resolution of the myocardial inflammation by methyl-prednisolone. These two cases actually indicate that myocarditis may develop into post-myocarditis dilated cardiomyopathy.

The mechanisms by which myocarditis progresses into dilated cardiomyopathy are still uncertain.<sup>16)</sup> Several possible pathogenesis of post-myocarditis dilated cardiomyopathy have been proposed from experimental studies, such as a persistent viral infection, inappropriate defensive response and autoimmune myocardial injury.<sup>7-15)</sup> We could not define the pathogenesis in the present two cases. Because these cases revealed a monophasic clinical course and responded to steroid therapy, neither the transition of pathogenesis nor the persistence of a virus is likely.<sup>17)</sup> The present cases suggested that extensive myocardial damages and the persistence of myocardial inflammation are possibly involved in the pathogenesis of post-myocarditis dilated cardiomyopathy.

The usefulness of immunosuppressive therapy for myocarditis is still controversial.<sup>18-22)</sup> Some patients with myocarditis respond favorably to steroid therapy, but others do not or their condition worsens. Discrimination between a responder and non-responder during the active phase of myocarditis is critically important,<sup>23,24)</sup> but no reliable methods for this discrimination has been established. We employed large dosages and short duration therapy using methylprednisolone, i.e. pulse therapy, in these two cases. Pulse therapy is an alternative method to discriminate the responder of steroid therapy and is possibly useful to avoid harmful effects of immunosuppressive therapy in myocarditis.

These two cases of acute and persistent myocarditis actually revealed the presence of post-myocarditis dilated cardiomyopathy. Steroid pulse therapy is useful in some patients with persistent myocarditis.

**Acknowledgements.** This study was in part supported by a grant to the Research Committee for Epidemiology and Etiology of Idiopathic Cardiomyopathy from the Ministry of Health and Welfare, Japan.

## REFERENCES

- 1) Kasper EK, Agema WRP, Hutchins GM, Deckers JW, Hare JM, Baughman KL: The causes of dilated cardiomyopathy: a clinicopathologic review of 673 consecutive patients. *J Am Coll Cardiol* **23**: 586-90, 1994.
- 2) Braunwald E: Heart disease: a textbook of cardiovascular medicine 4th edition, W.B. Saunders, Philadelphia 1992, p 1425-1438.
- 3) Dee Jr GW, Palacios IF, Fallon JT, Aretz HT, Mills J, Lee DC-S, Johnson RA: Active myocarditis in the spectrum of dilated cardiomyopathies. Clinical features, histologic correlates, and clinical outcome. *N Engl J Med* **312**: 885-90, 1985.
- 4) Zee-Cheng C, Tsai CC, Palmer DC, Codd JE, Pennington DG, Williams GA: High incidence of myocarditis by endomyocardial biopsy in patients with idiopathic congestive cardiomyopathy. *J Am Coll Cardiol* **3**: 63-70, 1984.
- 5) Fenoglio Jr JJ, Ursell PC, Kellogg CF, Drusin RE, Weiss MB: Diagnosis and classification of myocarditis by endomyocardial biopsy. *N Engl J Med* **308**: 12-18, 1983.
- 6) Remes J, Helin M, Vaino P, Rautio P: Clinical outcome and left ventricular function 23 years after Coxsackie virus myopericarditis. *Eur Heart J* **11**: 182-188, 1990.
- 7) Bowles NE, Richardson PJ, Olsen EGJ, Archard LC: Detection of Coxsackie-B-virus-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. *Lancet*: 1120-1122, 1986.
- 8) Klingel K, Hohenadl C, Canu A, Albrecht M, Seemann M, Mall G, Kandolf R: Ongoing enterovirus-induced myocarditis is associated with persistent heart muscle infection: quantitative analysis of virus replication, tissue damage, and inflammation. *Proc Natl Acad Sci USA* **89**: 314-318, 1992.
- 9) Why HJF, Meany BT, Richardson PJ, Olsen EGJ, Bowles NE, Cunningham L, Freeke CA, Archard LC: Clinical and prognostic significance of detection of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy. *Circulation* **82**: 2582-2589, 1994.
- 10) Woodruff JF, Woodruff JJ: Involvement of T lymphocytes in the pathogenesis of Coxsackie virus B-3 heart disease. *J Immunol* **13**: 1726-1734, 1974.
- 11) Wong CY, Woodruff JJ, Woodruff JF: Generation of cytotoxic T lymphocytes during Coxsackie B-3 infection. *J Immunol* **118**: 1159-1164, 1977.
- 12) Huber SA, Job LP, Woodruff JF: Lysis of infected myofibers by Coxsackievirus B-3-immune T lymphocytes. *Am J Pathol* **98**: 681-694, 1980.
- 13) Caforio ALP, Keeling PJ, Zachara E, Mestroni L, Camerini F, Mann JM, Bottazzo GF, McKenna WJ: Evidence from family studies for autoimmunity in dilated cardiomyopathy. *Lancet* **344**: 773-777, 1994.
- 14) Schwimmbeck PL, Badorff C, Schultheiss H-P, Strauer BE: Transfer of human myocarditis into severe combined immunodeficiency mice. *Circ Res* **75**: 156-164, 1994.
- 15) Kodama M, Hanawa H, Saeki M, Hosono H, Inomata T, Suzuki K, Shibata A: Rat dilated cardiomyopathy after autoimmune giant cell myocarditis. *Circ Res* **75**: 278-284, 1994.
- 16) Dec GW, Fuster V: Idiopathic dilated cardiomyopathy. *N Engl J Med* **331**: 1564-1575, 1994.
- 17) Tomioka N, Kishimoto C, Matsumori A, Kawai C: Effects of prednisolone on acute viral myocarditis in mice. *J Am Coll Cardiol* **7**: 868-872, 1986.
- 18) Mason JW, Billingham ME, Ricci DR: Treatment of acute inflammatory myocarditis assisted by endomyocardial biopsy. *Am J Cardiol* **45**: 1037-1044, 1980.
- 19) Daly K, Richardson PJ, Olsen EG, Morgan-Capner P, McSorley C, Jackson G, Jewitt DE: Acute myocarditis: role of histological and virological examination in the diagnosis and assessment of immunosuppressive treatment. *Br Heart J* **51**: 30-35, 1984.
- 20) Hosenpud JD, McAnulty JH, Niles NR: Lack of objective improvement in ventricular systolic function in patients with myocarditis treated with azathioprine and prednisone. *J Am Coll Cardiol* **6**: 797-801, 1985.
- 21) O'Connell JB, Reap EA, Robinson JA: The effects of cyclosporine on acute murine Coxsackie B3 myocarditis. *Circulation* **73**: 353-359, 1986.
- 22) Monrad ES, Matsumori A, Murphy JC, Fox JG, Crumpacker CS, Abelmann WH: Therapy with cyclosporine in experimental murine myocarditis with encephalomyocarditis virus. *Circulation* **73**: 1058-1064, 1986.
- 23) Kodama M, Zhang S, Hanawa H, Shibata A: Immunohistochemical characterization of infiltrating mononuclear cells in the rat heart with experimental autoimmune giant cell myocarditis. *Clin Exp Immunol* **90**: 330-335, 1992.
- 24) Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL: Clinicopathologic description of myocarditis. *J Am Coll Cardiol* **18**: 1617-1626, 1991.