Interferon Treatment for Dilated Cardiomyopathy and Striated Myopathy Associated With Hepatitis C Virus Infection Based on Serial Measurements of Serum Concentrations of Cardiac Troponin T

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The present authors recently suggested, on the basis of studies using polymerase chain reaction (PCR), that hepatitis C virus (HCV) infection is involved in the etiology or pathogenesis of cardiomyopathic disorders. They have also reported that the serum concentration of cardiac troponin T is an indicator of ongoing myocyte degeneration in patients with dilated cardiomyopathy (DCM) and hypothesized that its serial measurement may be a marker of therapeutic efficacy. This is the first case report of DCM and striated myopathy, associated with HCV infection, treated with interferon therapy guided by monitoring of serial serum concentrations of cardiac troponin T. Positive-plus strands of HCV RNA were found in the patient's myocardium, as well as plus and minus strands in the quadriceps muscle specimens. Serum levels of creatine kinase (CK), CK-MB and cardiac troponin T fell as serum HCV titers decreased during treatment with interferon, whereas conventional treatment of heart failure had no effect. Monitoring of serial serum concentrations of cardiac troponin T may allow the earlier diagnosis and treatment of patients with HCV-associated cardiomyopathy and improve their clinical course. (Jpn Circ J 2000; 64: 321–324)

Key Words: Dilated cardiomyopathy; Hepatitis C; Interferon; Troponin T; Heart failure

Hepatitis C virus (HCV), an RNA virus, was originally identified as the cause of non-A, non-B hepatitis. It was later reported that chronic HCV infection may be associated with other syndromes, including mixed cryoglobulinemia, polyarteritis nodosa, sicca-like syndrome and membranous proliferative glomerulonephritis. We recently suggested, on the basis of studies using polymerase chain reaction (PCR), that HCV infection is involved in the etiology or pathogenesis of cardiomyopathic disorders, although most of these patients have no signs of hepatitis.1–6 We have also reported that serum concentrations of cardiac troponin T are an indicator of ongoing myocyte degeneration in patients with dilated cardiomyopathy (DCM)7,8 and hypothesized that cardiac troponin T may be a marker of therapeutic efficacy in patients with non-ischemic heart disease.9 However, a specific treatment for HCV-associated cardiomyopathy has not been previously described, and the clinical criterion for following such patients has not been established. We report here the first case of DCM and striated myopathy associated with HCV infection in the absence of clinical findings of hepatitis, treated with interferon therapy guided by the monitoring of serial serum concentrations of cardiac troponin T.

Case Report
A 61-year-old woman was hospitalized in April 1995, complaining of general malaise and dyspnea. She had no history of infective myocarditis, toxic reaction, or metabolic or neuromuscular disease, and her family history was unremarkable. Her chest roentgenogram showed a cardiothoracic ratio of 55%, and the scalar electrocardiogram showed left axis deviation with intraventricular conduction delay. Echocardiography showed a dilated left ventricle, with an end diastolic dimension of 55 mm, and a left ventricular ejection fraction (LVEF) reduced to 45%. Measurements of serum alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase were normal. Serum creatine kinase (CK) was increased to 293 IU/L (normal, <160), with 95% MM isoenzyme. Serum concentrations of cardiac troponin T were increased to 0.18 ng/ml (normal, <0.02).6 C-reactive protein was negative and there were no clinical findings consistent with a diagnosis of connective tissue disease. An electromyogram of the quadriceps muscle showed polyphasic waves. Hypothyroidism was excluded by appropriate hormonal assays. She had a history of blood transfusion when she underwent surgery at the age of 43 for uterine myoma, and her serum anti-HCV antibody and HCV RNA in the serum were both positive; the HCV genotype was 1b. Abdominal ultrasonography showed no liver enlargement or atrophy.

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There was no significant increase in serum titers consistent with influenza virus A or B, Coxsackie virus A4,7,9,16 or B1,2,3,4,5,6, or with echovirus 3,7,11,12.

Additional investigations included cardiac catheterization and angiography, and endomyocardial and quadriceps muscle biopsies. Coronary angiography showed no significant coronary stenosis and left ventriculography showed a dilated left ventricle and depressed ejection fraction. Microscopic examination showed the presence of myocyte degeneration and interstitial fibrosis. The quadriceps muscle biopsy showed degeneration of striated muscle cells and fibrosis. PCR assays for HCV were performed as reported previously. Plus and minus strands of HCV RNA were positive in the quadriceps muscle biopsies. She was discharged from the hospital with a diagnosis of DCM and striated myopathy, on a regimen of diuretics and digoxin.

Despite being compliant with her medications for chronic heart failure, the patient began to suffer from severe general malaise and dyspnea. Echocardiography was repeated and showed worsening of the LVEF to 34% and a further increase in the left ventricular end diastolic dimension to 66 mm. Serial measurements of CK enzyme and cardiac troponin T serum concentrations over the 3-year period revealed that they remained increased at 244–638 IU/L, and 0.11–0.15 ng/ml, respectively, and conventional management of heart failure using furosemide, spironolactone, dopamine, dobutamine, digoxin, angiotensin converting enzyme inhibitor and β-blocker failed to decrease the serum concentrations of either. Because minus HCV RNA strands are considered intermediate in the replication of the HCV genome, we suspected that this case of DCM and myopathy was caused by HCV infection. Interferon has been found effective as a treatment of patients with HCV infection\(^\text{10,11}\) and we had showed its efficacy in an animal model of viral myocarditis.\(^\text{12}\) Despite its known potential for causing adverse cardiac effects,\(^\text{13}\) the decision was made to use interferon-\(\alpha\) after obtaining the patient's informed consent.

The patient was rehospitalized, monitored, and placed on a continuous infusion of lidocaine and isosorbide dinitrate as prevention against serious ventricular arrhythmias and coronary spasm. Treatment with interferon-\(\beta\) was started with a dose of 1×10^6 U/day for 2 days, 3×10^6 U/day for 2 days, and 6×10^6 U/day for 8 days. The treatment had to be terminated on day 12 because of profound general malaise and poor overall condition. However, the serum concentrations of CK, CK-MB and cardiac troponin T decreased as HCV RNA concentrations fell, and the persistently elevated CK enzyme normalized for the first time (Fig.1). All measurements reverted toward the baseline after cessation of interferon. During this brief period, the patient's physical condition, including heart rate, blood pressure and body weight, was stable, and the chest roentgenogram and echocardiogram remained unchanged. No adverse cardiac effects of interferon were noted.

After cessation of interferon therapy, conventional heart failure therapy was resumed. However, the CK enzyme and cardiac troponin T serum concentrations rose again and remained increased between 264 and 671 IU/L, and 0.12 and 0.30 ng/ml, respectively. The patient died from worsening of chronic heart failure in June 1999, 10 months after discontinuation of interferon. At autopsy, the heart weight was 450 g and the left ventricular transverse dimension was 62 mm. The thickness of the left ventricular interseptal and posterior wall was 11 mm and 8 mm, respectively, with massive interstitial fibrosis. Microscopic examination of the myocardium showed myocyte degeneration, interstitial fibrosis, and infiltration by a few mononucleate cells (Fig.2), which immunohistochemistry revealed to be mostly T cells. Strands of HCV RNA+ were positive in these postmortem myocardial specimens. Examination of the quadriceps muscle showed severe degeneration of striated muscle.
cells caused by atrophy and fibrosis (Fig 3). In the liver, spill over of inflammatory cells from the portal tract into the periportal region was minimal and the morphology was of chronic venous congestion.

**Discussion**

We recently became suspicious of the participation of HCV in the etiology and pathogenesis of DCM after finding a high incidence of anti-HCV antibodies in the serum of patients suffering from cardiomyopathy, and after confirmation of positive HCV gene by PCR in some of the myocardial specimens. Okabe et al described the relationship between HCV infection and chronic myocarditis with dilated left ventricle and decreased left ventricular ejection fraction, which resembles DCM. Furthermore, myopathy in the presence of chronic HCV infection has been described in other case reports. In the present patient, strands of HCV RNA+ in the heart tissue, as well as plus- and minus-strands in the quadriceps muscle tissue, were positive. The serum concentrations of CK and cardiac troponin T remained abnormally high over the 3-year period, but fell in parallel with the decline in serum HCV RNA during treatment with interferon. Conventional treatment for heart failure had no effect on these measurements. To the best of our knowledge, this is the first case of DCM and striated myopathy associated with HCV infection that has been treated with interferon. Many different HCV-sequences have been reported worldwide and, in the blood of a given patient infected with HCV, a population of closely related mutants, termed quasispecies, is observed. Interruption of the cardiac specific clone may lead to clinical improvement, or may prevent the exacerbation of symptoms of heart failure, in patients with HCV-associated cardiomyopathy.

We recently reported that patients with DCM whose prognosis is poor have abnormally high serum concentrations of cardiac troponin T, although serum concentrations of CK remain in the normal range, and that, in this population, the serum concentrations of cardiac troponin T are a
prognostic marker? It is noteworthy that most patients with a poor prognosis had persistently high serum concentrations of cardiac tropinin T, even when they had been compensated by conventional treatment of heart failure and were free of dyspnea or roentgenographic and auscultatory pulmonary congestion! Measurement of serial serum concentrations of cardiac tropinin T is not just a marker of heart failure, but seems to be a reliable immunopathologic indicator of subclinical, ongoing myocyte degeneration. Our hypothesis is that treatment of heart failure that ultimately improves the prognosis is associated with a fall in the serum concentration of cardiac tropinin T. Unfortunately in the present case, interferon therapy had to be terminated because of general malaise, before a clinical improvement could be observed. However, earlier diagnosis and treatment based on the serial monitoring of serum concentrations of cardiac tropinin T may improve the clinical course of patients with HCV-associated cardiomyopathy. Further studies are necessary to elucidate the timing, dosage and adverse cardiac effects of interferon therapy.

References
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