7 Role of Hepatitis C Virus in Cardiomyopathies

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Abstract. Virus infection was conventionally considered to cause myocarditis, which resulted in development of dilated cardiomyopathy. Recent studies suggest that hepatitis C virus (HCV) is involved in the development of dilated cardiomyopathy, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy in addition to myocarditis. Furthermore, left ventricular aneurysm represents the same morbid state not only after myocardial infarction but also after myocarditis. There were wide variations in the frequency of detection of HCV genomes in cardiomyopathies in different regions or in different populations. Major histocompatibility complex class II genes may play a role in the susceptibility to HCV infection, and may influence the development of

different phenotypes of cardiomyopathies. If it is the fact that the myocardial damage is caused by HCV, it might be expected that interferon (IFN) treatment would be useful for its treatment. Patients receiving IFN treatment of hepatitis were screened by thallium myocardial scintigraphy, and an abnormality was discovered in half of patients. Treatment with IFN resulted in disappearance of the image abnormality. It has thus been suggested that mild myocarditis and myocardial damage may be cured with IFN. We have recently found that high concentrations of circulating cardiac troponin T are a specific marker of cardiac involvement in HCV infection. By measuring cardiac troponin T in patients with HCV infection, the prevalence of cardiac involvement in hepatitis C virus infection will be clarified. We are proposing a collaborative work on global network on myocarditis/cardiomyopathies due to HCV infection.

7.1 Introduction

Cardiomyopathies may present as idiopathic dilated, hypertrophic or restrictive disease, arrhythmogenic right ventricular cardiomyopathy or several other distinct disorders of the heart muscle (Richardson et al. 1996). Dilated cardiomyopathy, hypertrophic cardiomyopathy and restrictive cardiomyopathy are heterogeneous myocardial disorders of multifactorial aetiologies, including genetic anomalies and acquired immune pathogenetic factors, such as viral infections (Matsumori 1997). Dilated cardiomyopathy is a relatively common myocardial disorder, which may lead to severe heart failure. Along with ischaemic heart disease, it represents the main antecedent of heart transplantation in Western countries, where epidemiological studies performed a decade ago have measured 5-year survival rates as low as 30% to 40% after its initial diagnosis. In contrast, few large-scale studies have been conducted to examine the prevalence, prognosis and management patterns of cardiomyopathies in Asian populations.

Recently, nationwide clinico-epidemiological surveys of cardiomyopathies were performed in Japan (Miura et al. 2002; Matsumori et al. 2002). The total number of patients was estimated at 17,700 (prevalence; 14.0 per 100,000) for dilated cardiomyopathy, 21,900 (17.3 per 100,000) for hypertrophic cardiomyopathy, 300 (0.2 per 100,000) for restrictive cardiomyopathy and 520 (0.4 per 100,000) for arrhythmogenic right ventricular cardiomyopathy. The prevalence of dilated cardiomyopa-

thy and hypertrophic cardiomyopathy was higher in men than women: the men-to-women ratios were 2.6 and 2.3 for dilated cardiomyopathy and hypertrophic cardiomyopathy, respectively. The occurrence of cardiomyopathies was most frequent in the age range of 60–69 years both in dilated cardiomyopathy and in hypertrophic cardiomyopathy.

7.2 Role of Viruses in the Pathogenesis of Cardiomyopathies

The myocardium is involved in a wide range of viral infections. In some cases, myocarditis may be the primary disorder; in others, it may occur as part of a systemic disease. Myocarditis is thought to be most commonly caused by enteroviruses, particularly coxsackievirus B. However, in many cases, when myocarditis has been diagnosed on the basis of clinical characteristics, no definite confirmation of viral origin is obtained, despite extensive laboratory investigations. The evidence is often only circumstantial and a direct, conclusive proof of cardiac involvement is not available (Kawai et al. 1987; Abelmann and Lorell 1989; Olinde and O'Connell 1994). However, accumulating evidence links viral myocarditis with the eventual development of dilated cardiomyopathy (Johnson and Palacios 1982; Matsumori and Kawai 1982a,b; Caforio et al. 1990; Matsumori 1993; Feldman and McNamara 2000; Liu and Mason 2001).

The clinical presentation of viral myocarditis is variable. When myocardial necrosis occurs diffusely, congestive heart failure develops and, later, dilated cardiomyopathy. If myocardial lesions are localized, a ventricular aneurysm may form. When complicated with arrhythmias, myocarditis presents as arrhythmogenic right ventricular cardiomyopathy (Matsumori 1993). When myocardial necrosis is localized to the subendocardium, restrictive cardiomyopathy may develop. While it has not been established that hypertrophic cardiomyopathy may be a complication of viral myocarditis, asymmetrical septal hypertrophy has, in fact, sometimes been observed in patients with myocarditis (Fig. 1; Kawano et al. 1994).

The myocardium may be the target of several types of viral infections. Recently, the importance of hepatitis C virus (HCV) has been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy and myocarditis and myocarditis (Matsumori et al. 1995, 1996, 1998a,b,

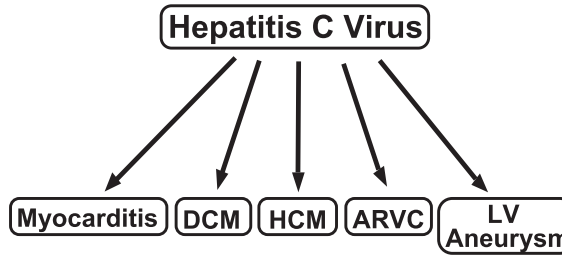

Fig. 1. Hepatitis C virus causes various heart diseases. *ARVC*, arrhythmogenic right ventricular cardiomyopathy; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *LV*, left ventricle

1999, 2000; Matsumori 1997, 2001, 2003, 2005; Okabe et al. 1997; Takeda et al. 1999; Ooyake et al. 1999; Sato et al. 2000; Nakamura et al. 2000). In a collaborative research project of the Committees for the Study of Idiopathic Cardiomyopathy in Japan, HCV antibody was found in 74 of 697 patients (10.6%) with hypertrophic cardiomyopathy and in 42 of 663 patients (6.3%) with dilated cardiomyopathy; this prevalence in patients with cardiomyopathies was significantly higher than in age-matched volunteer blood donors in Japan (2.4%).

The global prevalence of HCV carriers is estimated to average 3%, ranging from 0.1% to 10% or more in different countries (Cohen 1999). In Europe, the overall prevalence is 1% with a north-south gradient, ranging from 0.5% in northern countries to 2% in Mediterranean countries. Recent studies have shown high prevalence in Eastern Europe, ranging from 0.7% to 5%. There are 170 million chronic HCV carriers throughout the world, of whom an estimated 2 million are in Japan, 2.7 million in the United State and 5 million in Western Europe.

Until relatively recently, blood transfusion posed a major risk of HCV infection in developed countries. The introduction in 1989 and 1992 of improved blood-screening tests by the detection of anti-HCV infection (Beld et al. 2000) changed this.

7.3 HCV Infection and Cardiomyopathies

We first evaluated 31 patients with cardiomyopathy and myocarditis by polymerase chain reaction (PCR) for the presence of RNA viruses such as enterovirus, cardiovirus, hepatitis A virus, human immunodeficiency viruses (HIV)1 and 2, human T lymphocytic leukaemia virus (HTLV) I, influenza A and B viruses, and reovirus. We also evaluated patients with cardiomyopathy and myocarditis for DNA viruses such as adenovirus, cytomegalovirus, Epstein-Barr virus, hepatitis B virus, human herpesvirus 6, varicella-zoster virus, and herpes simplex virus types 1 and 2. However, enterovirus RNA was detected in only one (3.2%) patient with dilated cardiomyopathy, and no other virus genomes were found. On the other hand, we found HCV RNA in six patients (19.4%) with dilated cardiomyopathy (Matsumori et al. 1995; Table 1).

7.3.1 HCV Infection and Dilated Cardiomyopathy

Over a 10-year period, we identified 19 of 191 patients (9.9%) with dilated cardiomyopathy who had evidence of HCV infection on the basis of a positive immunoradiometric assay, whereas only 1 of 40 patients (2.5%) of those with ischaemic heart disease was positive for the HCV antibody (Matsumori 2005). Since the prevalence of positive HCV antibody in voluntary blood donors in Japan was 2.4% in subjects 55 to

Table 1. PCR analysis for RNA viruses in the hearts of patients with myocarditis and cardiomyopathy

Virus	Positive (n)/total $n = 31$ (%)
Cardiovirus	0
Enterovirus (coxsackievirus B)	1 (3.2%)
Hepatitis A	0
Hepatitis C	6 (19.4%)
HIV 1 and 2	0
HTLV-1	0
Influenza A	0
Influenza B	0
Reovirus	0

59 years of age, the difference was statistically significant (Table 2). None of the patients with HCV antibody had a history of intravenous drug use. Mildly elevated levels of serum aminotransferase were found in some of the patients who had blood transfusions. Three patients had a history of hepatitis, and mildly elevated serum aminotransferase was measured in 10 patients. The primary findings at presentation were heart failure and cardiac arrhythmias. Of the 19 patients with HCV antibodies, 10 patients had HCV RNA in the serum, and all 6 patients had type 1b HCV (Table 3).

Quantitative analysis of HCV RNA showed that the copy number in the serum was 8×10^2 to 1.2×10^6 copies/ml. HCV RNA was found in the heart of 8 patients. Negative strands of HCV RNA were detected in the heart of 2 patients. Because negative RNA molecules are considered to be intermediates in the replication of the HCV genome, it is supposed that HCV replicates in myocardial tissues.

Table 2. Frequency of HCV antibody in patients with cardiomyopathies at Kyoto University

Positive (n)		Total (n)	Frequency
Dilated cardiomyopathy	19	191*	9.9%
Hypertrophic cardiomyopathy	16	113*	14.1%
ARVC	1	2	50.0%

ARVC, arrhythmogenic right ventricular cardiomyopathy
*$p < 0.0001$ vs volunteer blood donors; 2.4% (24 of 1,039)

Table 3. Clinical features of dilated cardiomyopathy associated with HCV infection

Cases	$n = 19$
Age, sex	62 ± 15yo (17–83) M:10, F:9
PH	Hepatitis 3
	Elevated aminotransferase 10
HCV type	1b, 7; 2, 3
Titre	8×10^2–1.2×10^6 copies/ml
HCV RNA in the heart	(+) Strands 8/13, (–) strands 2/8

7.3.2 HCV Infection and Hypertrophic Cardiomyopathy

Over a 10-year period, 16 of 113 patients (14.1%) with hypertrophic cardiomyopathy were identified who had evidence of HCV infection on the basis of positive HCV antibody (Table 2). When compared with the prevalence of positive HCV antibody in voluntary blood donors, the difference was statistically significant. Of these 16 patients, none of the patients had a family history of hypertrophic cardiomyopathy. Seven patients had hepatoma, 4 patients had blood transfusions, and mildly elevated serum aminotransferases were measured in 10 patients. Nine patients had ace of spade-shaped deformities of the left ventricle with a ratio of apical thickness to middle anterior free wall thickness exceeding 1.3, and were diagnosed as apical hypertrophic cardiomyopathy (Matsumori 2005). None had angiographically visible coronary artery disease.

Histopathological studies showed mild to severe degrees of myocyte hypertrophy in the right or left ventricle, and mild to moderate fibrosis, and mild cellular infiltration was seen. Type 1b HCV RNA was detected in the serum of 7 patients. Quantitative analysis of HCV RNA showed that the copy number in the serum was 5.5×10^3 to 4×10^6 copies/ml. HCV RNA was found in the biopsy specimens of 6 patients. Negative strands of hepatitis C virus RNA were found in the hearts of 2 patients (Table 4). Analysis by fluorescent single-stand conformation

Table 4. Clinical features of hypertrophic cardiomyopathy associated with HCV infection

Cases	$n = 16$
Age, sex	65 ± 10yo (50–81) M:9, F:7
PH	Hepatoma 7, blood transfusion 4
	Elevated aminotransferase 10
Type	ASH 9, APH 5, obstructive 3
HCV type	1b, 7; 2, 3
Titre	5.5×10^3–4×10^6 copies/ml
HCV RNA in the heart	(+) Strands 6/8, (–) strands 2/6

APH, apical hypertrophy; ASH, asymmetrical septal hypertrophy; PH, past history

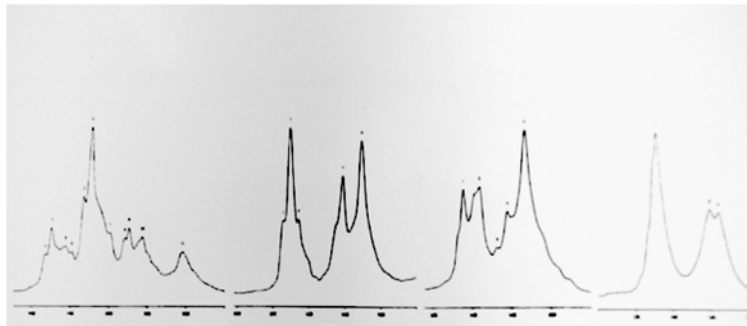

Fig. 2. Analysis by fluorescent single-stranded conformation polymorphism of sera from 4 patients with cardiomyopathy. The presence of multiple clones in the sera is shown

polymorphism showed the presence of multiple clones in the sera of patients with hypertrophic cardiomyopathy (Fig. 2).

Recently, Teragaki and co-workers studied the prevalence of HCV infection in 80 Japanese patients with hypertrophic cardiomyopathy, and found that 22.5% of the patients were positive for HCV antibody. When compared with controls, the difference was statistically significant. In their study, 7 patients had HCV type 1b, and 5 patients had type 2a (Teragaki et al. 2003). The prevalence of HCV infection in their study was more frequent than that of our study.

7.3.3 HCV Infection and Heart Diseases: A Multicentre Study in Japan

As shown above, hypertrophic and dilated cardiomyopathies were both associated with significantly higher prevalences of positive antibodies than was measured among blood donors. In addition, positive HCV antibody was more prevalent in patients with hypertrophic cardiomyopathy than in those with dilated cardiomyopathy. Positive HCV antibody was detected in 650 of 11,967 patients (5.4%) seeking care at five university hospitals, a significantly higher prevalence than in volunteer blood donors. Of the cardiac abnormalities observed in these patients with positive HCV antibody, arrhythmias were the most frequent (21.5%).

Electrocardiographic abnormalities were found in 130 of 349 patients tested (62.8%), most often in the form of arrhythmias or conduction disturbances (Matsumori et al. 1998a). Echocardiographic examination suggested that HCV infection was associated with left ventricular hypertrophy in over one half of the patients, ventricular dilatation in 40% and decreased left ventricular systolic function in 34%.

The study suggests that several cardiac abnormalities other than cardiomyopathic disorders (e.g. arrhythmias) may result from HCV infection, which may be a risk factor for such conditions (hypertension, myocardial infarction, etc.; Table 5), although further study is necessary to confirm these associations. More recently, a possible role of HCV infection in the pathogenesis of atherosclerosis has been reported (Ishizaka et al. 2002).

Table 5. Clinical diagnoses of patients with HCV antibody

Clinical diagnoses	n (total $n = 349$)	Frequency (%)
Arrhythmia	75	21.5
Hypertension	71	20.3
Myocardial infarction	57	16.3
Diabetes mellitus	50	14.3
Angina pectoris	45	12.9
Renal disease	41	11.7
Valvular heart disease	33	9.5
Congestive heart failure	28	8.0
Hypertrophic cardiomyopathy	23	6.6
Post valvular replacement and/or CABG	22	6.3
Dilated cardiomyopathy	20	5.7
Cerebrovascular disease	7	2.0
Unclassified cardiomyopathy	2	0.6
Myocarditis	1	0.3

CABG, coronary artery bypass grafting
(Reproduced from Matsumori et al. 1998a with permission of Japan Circulation Society)

7.3.4 HCV Genomes from Paraffin Heart Sections

A collaborative multicentre study was performed by the Scientific Council on Cardiomyopathies of the World Heart Federation to test the reproducibility of detection of viral genomes, such as enteroviruses, adenovirus, cytomegalovirus and HCV in formalin-fixed tissues. In this study, autopsy and biopsy materials were analysed blindly. We found HCV genomes in 2 out of 11 hearts (18%) of patients with dilated cardiomyopathy and myocarditis from Italy, and in 4 out of 11 hearts (36%) from the United States, two of which were from patients with myocarditis, and the other two from patients with arrhythmogenic right ventricular cardiomyopathy. The results suggest that HCV may cause arrhythmogenic right ventricular cardiomyopathy as well as myocarditis, dilated cardiomyopathy and hypertrophic cardiomyopathy. As the detection of HCV genomes in formalin-fixed sections seems less sensitive than in frozen sections, HCV infection may actually be a more prevalent cause of myocardial injury.

In a collaborative research project with the National Cardiovascular Center and Juntendo University, we have tried detecting HCV genomes in paraffin sections of autopsied hearts. Among 106 hearts examined, β-actin gene was amplified in 61 (52.6%). Among these, HCV RNA was detected in 13 (21.3%), and negative strands in 4 hearts (6.6%). HCV RNA was found in 6 hearts (26.0%) with hypertrophic cardiomyopathy, 3 hearts (11.5%) with dilated cardiomyopathy and 4 hearts (33.3%) with myocarditis (Table 6). These HCV RNA-positive samples were obtained between 1979 and 1990, indicating that HCV RNA can be amplified from paraffin-embedded hearts preserved for many years (Matsumori et al. 2000).

We also analysed autopsied hearts with dilated cardiomyopathy from the University of Utah as a collaborative research project, and found HCV RNA in 8 of 23 hearts (35%) with positive actin genes (Table 7). The sequences of HCV genomes recovered from these hearts were highly homologous to the standard strain of HCV (Fig. 3). These observations lend support to the previous findings of an important role played by the HCV in the pathogenesis of hypertrophic cardiomyopathy and dilated cardiomyopathy. However, there were wide variations in the frequency of detection of HCV genomes in cardiomyopathy among different cities.

Table 6. Detection of hepatitis C virus genomes from the autopsied hearts of patients with myocarditis, and dilated and hypertrophic cardiomyopathies with positive-actin gene

Diagnosis	Positive, *n*	Frequency, %	*p* (Fisher)
Myocarditis	4/12	33.3%	0.0008
DCM	3/26	11.5%	0.034
HCM	6/23	26.0%	0.0005
Myocarditis+DCM+HCM	13/61	21.3%	0.0002
Controls*	0/52	0%	–

HCM, hypertrophic cardiomyopathy; IHD, ischemic heart disease *IHD $n = 32$, Non-cardiac death $n = 20$
(Reproduced from Matsumori et al. 2000, with permission of Nature Publishing Group)

Table 7. Detection of HCV genomes from the formalin-fixed paraffin sections of autopsied DCM hearts

	HCV genomes (+)	Total (%) (*n*)	HCV genomes (+)	Positive (%) Actin (*n*)
University of Utah	18/72	(25%)	8/23	(34.8%)
LDS Hospital, Utah	0/31	(0%)	0/12	(0%)
St. Paul's Hospital, Vancouver	0/24	(0%)	0/11	(0%)
Japan	5/50	(10%)	3/26	(11.5%)

HCV genomes were detected in none of 24 hearts from St. Paul's Hospital in Vancouver, Canada (Matsumori 2005). These results suggest that the frequency of cardiomyopathy caused by HCV infection may be different in different regions or in different populations. Some European investigators have reported negative associations between HCV infection and dilated cardiomyopathy, though the disparity in results may be due to inappropriate controls, incomplete clinical investigation or other factors such as regional or racial difference.

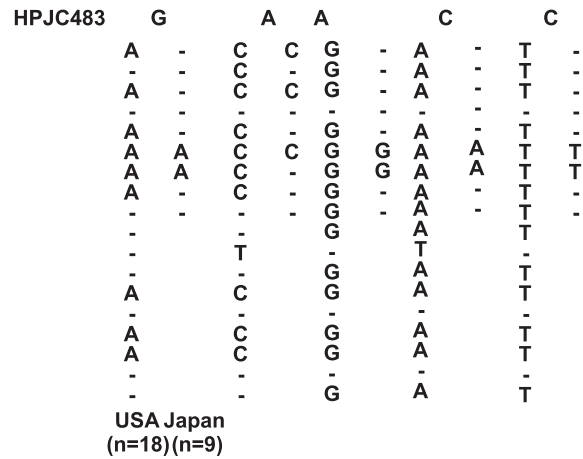

Fig. 3. Differences in the nucleotide sequences of HCV recovered from the hearts of cardiomyopathies obtained from Japan and the USA

7.3.5 Association of the Genes of the Major Histocompatibility Complex Class II with Cardiomyopathies Due to HCV Infection

The human major histocompatibility complex (MHC) is located on the short arm of chromosome 6 and encodes for several protein products involved in immune function, including complement, tumour necrosis factor (TNF)-α and the human leukocyte antigen (HLA) complex, whose polymorphisms are often proposed as candidate of susceptibility of various diseases. Associations of MHC class II antigens have been reported with patients with hypertrophic cardiomyopathies (Matsumori et al. 1981). More recently, MHC class II genes have also been analysed at the DNA level, though the results were inconsistent. In a Japanese study, the frequencies of DRB1*1401, DQB1*0503 and DRB1*1101 were increased in patients with dilated cardiomyopathy (Nishi et al. 1995). However, the development of dilated cardiomyopathy cannot be solely explained by the presence or absence of a single MHC class II allele. Since the aetiology of dilated cardiomyopathy is heterogeneous

(Matsumori 1997), different disease entities may be linked to different MHC class II genes.

Genetic studies to date have examined three aspects of HCV infection: (1) clearance, (2) progression (cirrhosis) and (3) susceptibility to infection. Recent studies on HCV hepatitis showed that DQB1*0301 was associated with clearance of the virus (Cramp et al. 1998; Alric et al. 1997). DRB1*04 and DQA1*03 were identified as protective alleles (Cramp et al. 1998), which are in strong linkage disequilibrium with DQB1*0301. DRB1*1101, which is also in linkage disequilibrium with DQB1*0301, was associated with clearance (Alric et al. 1997), and DRB1*11 was associated in other study. Several other studies have considered the association of MHC alleles with progression of liver disease. Two Japanese studies compared HCV carriers with normal liver function tests and normal histology with patients with abnormal liver function tests and cirrhosis, respectively (Kuzushita et al. 1998; Aikawa et al. 1996). In both studies, DQB1*0401, DRB1*0405 and a two-locus haplotype consisting of these alleles were more frequent in those who developed chronic liver disease.

We have recently studied association analyses of the distribution of alleles using phenotype frequencies in patients with hypertrophic or dilated cardiomyopathy and healthy controls. The frequency of HLA-DQB1*0303 was the most significantly increased in patients with hypertrophic cardiomyopathy (Table 8). HLA-DRB1*0901 was also significantly increased in patients with hypertrophic cardiomyopathy. However, there was no increase in either allele in patients with dilated cardiomyopathy. HLA-DRB1*1201 was slightly increased in patients with dilated cardiomyopathy, but not in patients with hypertrophic cardiomyopathy (Table 9, Fig. 4; Matsumori et al. 2003). MHC class II genes may play a role in the clearance of HCV and the susceptibility to HCV infection, and may influence the development of different phenotypes of cardiomyopathy.

7.3.6 Treatment of HCV Cardiomyopathies

In patients with HCV hepatitis, the success of treatment can be measured by the biochemical (normalization of alanine aminotransferase levels) and virological (undetectability of serum HCV RNA) responses.

Table 8. HLA alleles in 34 patients with hypertrophic cardiomyopathy associated with hepatitis C infection versus 136 control individuals

HLA allele	Patients		Control		RR	χ^2	*p*
	n	%	*n*	%			
DRB1*0101						0.10	
*0401	1	2.9	2	1.5	2.03	0.34	0.56
*0403	2	5.9	12	8.8	0.65	0.31	0.58
*0405	7	20.6	44	32.4	0.54	1.79	0.18
*0406	1	2.9	4	2.9	1.00	0.00	1
*0407	2	5.9	2	1.5	4.19	2.03	0.13
*0410	1	2.9	3	2.2	1.34	0.06	0.80
*0802	2	5.9	13	9.6	0.59	0.46	0.50
*0803	8	23.5	19	14.0	1.89	1.86	0.17
*0901	16	47.1	36	26.5	2.47	5.43	0.020
*1101	1	2.9	8	5.9	0.48	0.47	0.49
*1201	1	2.9	6	4.4	0.66	0.15	0.70
*1302	6	17.6	22	16.2	1.11	0.04	0.84
*1403	0	0	1	0.7	0.00	0.25	0.62
*1407	1	2.9	0	0	–	4.02	0.045
*1501	2	5.9	20	14.7	0.36	1.88	0.17
*1502	5	14.7	23	16.9	0.85	0.10	0.76
*1602	0	0	1	0.7	0.00	0.25	0.62
DQA1*0101	5	14.7	44	32.4	0.36	4.13	0.045
*0102	9	26.5	36	26.5	1.00	0.00	1
*0103	13	38.2	39	28.7	1.54	1.17	0.28
*0104	0	0	17	12.5	0.00	4.72	0.030
*0301	23	67.6	88	64.7	1.14	0.10	0.75
*0401	1	2.9	13	9.6	0.29	1.58	0.21
*0501	2	5.9	16	11.8	0.47	0.99	0.32
*0601	1	2.9	4	2.9	1.00	0.00	1
DQB1*0301	3	8.8	25	18.4	0.43	1.81	0.18
*0302	5	14.7	24	17.6	0.80	0.17	0.68
*0303	17	50.0	36	26.5	2.78	7.02	0.0081
*0401	7	20.6	43	31.6	0.56	1.59	0.21
*0402	2	5.9	8	5.9	1.00	0.00	1
*0501	5	14.7	27	19.9	0.70	0.47	0.49
*0502	2	5.9	10	7.4	0.79	0.09	0.76
*0601	13	38.2	38	27.9	1.60	1.37	0.24
*0602	1	2.9	19	14.0	0.19	3.19	0.074
*0604	6	17.6	22	16.2	1.11	0.04	0.84

RR, relative risk

Table 9. HLA alleles in 19 patients with dilated cardiomyopathy associated with hepatitis C virus infection versus 136 control individuals

HLA allele	Patients		Control		RR	χ^2	*p*
	n	%	*n*	%			
DRB1*0101	5	26.3	23	16.9	1.75	0.10	0.32
*0401	0	0	2	1.5	0.00	0.28	0.59
*0403	0	0	12	8.8	0.00	1.82	0.18
*0405	6	31.6	44	32.4	0.97	0.005	0.95
*0406	0	0	4	2.9	0.00	0.57	0.45
*0407	0	0	2	1.5	0.00	0.28	0.59
*0410	0	0	3	2.2	0.00	0.43	0.51
*0802	1	5.3	13	9.6	0.53	0.37	0.54
*0803	3	15.8	19	14.0	1.15	0.05	0.83
*0901	5	26.3	36	26.5	0.99	0.0002	0.99
*1101	2	10.5	8	5.9	1.88	0.60	0.44
*1201	3	15.8	6	4.4	4.06	3.95	0.047
*1302	0	0	22	16.2	0.00	3.58	0.058
*1403	1	5.3	1	0.7	7.50	2.68	0.10
*1407	0	0	0	0	–	–	–
*1501	3	15.8	20	14.7	1.09	0.02	0.90
*1502	4	21.1	23	16.9	1.31	0.20	0.66
*1602	1	5.3	1	0.7	7.50	2.68	0.10
DQA1*0101	5	26.3	44	32.4	0.75	0.28	0.60
*0102	6	31.6	36	26.5	1.28	0.22	0.64
*0103	7	36.8	39	28.7	1.45	0.53	0.47
*0104	0	0	17	12.5	0.00	2.67	0.10
*0301	12	63.2	88	64.7	0.94	0.02	0.89
*0401	1	5.3	13	9.6	0.53	0.37	0.54
*0501	3	15.8	16	11.8	1.41	0.25	0.62
*0601	0	0	4	2.9	0.00	0.57	0.45
DQB1*0301	3	15.8	25	18.4	0.83	0.08	0.78
*0302	0	0	24	17.6	0.00	3.97	0.046
*0303	6	31.6	36	26.5	1.28	0.22	0.64
*0401	6	31.6	43	31.6	1.00	0.00001	1.00
*0402	1	5.3	8	5.9	0.89	0.01	0.91
*0501	5	26.3	27	19.9	1.44	0.43	0.51
*0502	1	5.3	10	7.4	0.70	0.11	0.74
*0601	7	36.8	38	27.9	1.50	0.64	0.42
*0602	3	15.8	19	14.0	1.15	0.05	0.83
*0604	2	10.5	22	16.2	0.61	0.41	0.52

RR, relative risk

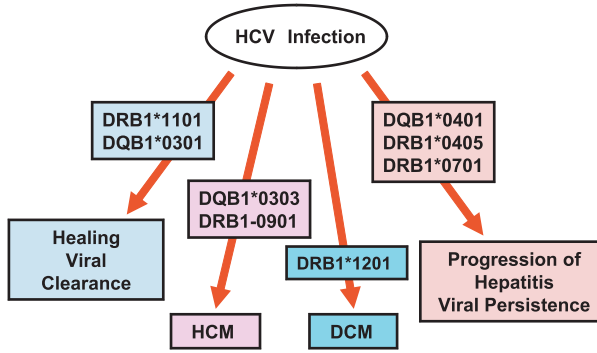

Fig. 4. Major histocompatibility complex genes and HCV infection

However, therapeutic markers to follow HCV cardiomyopathies have not been established in clinical practice. We have examined the effect of interferon on myocardial injury associated with active HCV hepatitis in collaboration with Shimane University. Since TL-201-SPECT is a more sensitive method than electrocardiography or echocardiography to detect myocardial injury induced by HCV, we used T1-SPECT scores to measure the effects of interferon on myocardial injury. SPECT scores improved in 8 out of 15 patients (53%) whose interferon treatment was completed. Circulating HCV disappeared after interferon therapy in all 11 patients, with either a decrease or no change in SPECT scores, but HCV genomes persisted in the blood in 2 patients whose clinical status worsened (Ooyake et al. 1999). This preliminary study suggests that interferon is a promising treatment for myocardial diseases caused by HCV infection.

We have recently reported that patients with dilated cardiomyopathy whose prognosis is poor have abnormally high serum concentrations of cardiac troponin T in the absence of an increase in serum creatine kinase concentrations, and that, in that population, cardiac troponin T is a prognostic marker (Sato et al. 2001). Serial measurements of serum cardiac troponin T concentrations seem to be a reliable indicator of myocyte injury, and we have hypothesized that, in patients with cardiomyopathy, therapeutic interventions for heart failure which ultimately improve the prognosis, should be associated with a fall in cardiac troponin T.

Therefore, in patients with HCV cardiomyopathies, monitoring of HCV RNA and cardiac troponin T appears appropriate.

We have reported the treatment with interferon for a patient with dilated cardiomyopathy and striated myopathy associated with HCV infection, guided by serial measurements of serum HCV RNA and cardiac troponin T (Sato et al. 2000). In that patient, serum concentrations of cardiac troponin T remained abnormally high over a 3-year period despite treatment of heart failure with angiotensin-converting enzyme inhibitors, β-adrenergic blockers, calcium antagonists, dopamine and dobutamine. Clinical manifestations of heart failure progressed, while echocardiographic left ventricular ejection fraction decreased from 49% to 29%, and left ventricular end-diastolic dimension increased from 60 mm to 69 mm. HCV RNA in heart tissue was positive by PCR. Interferon therapy was introduced with monitoring of cardiac troponin T concentration, which fell in parallel with a decline in serum HCV RNA during treatment. It is also noteworthy that, after cessation of interferon therapy, serum concentrations of cardiac troponin T and serum HCV RNA returned toward their baseline values (Sato et al. 2000; Fig. 5, left). These observations strongly suggest that the myocyte injury documented in

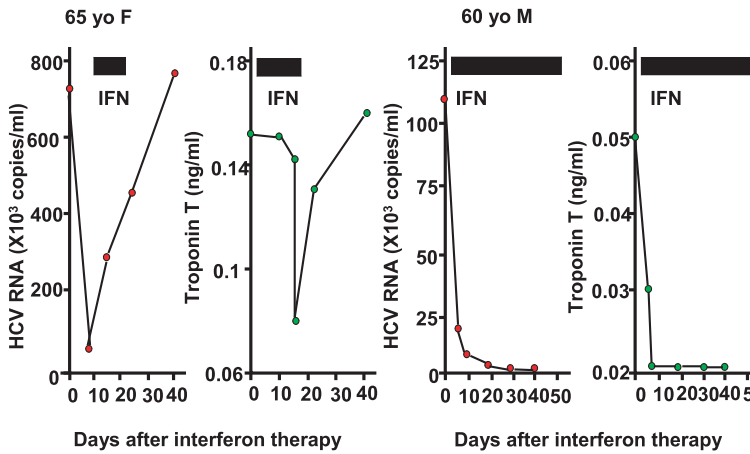

Fig. 5. Interferon therapy in patients with HCV cardiomyopathy guided by serum HCV RNA and cardiac troponin T

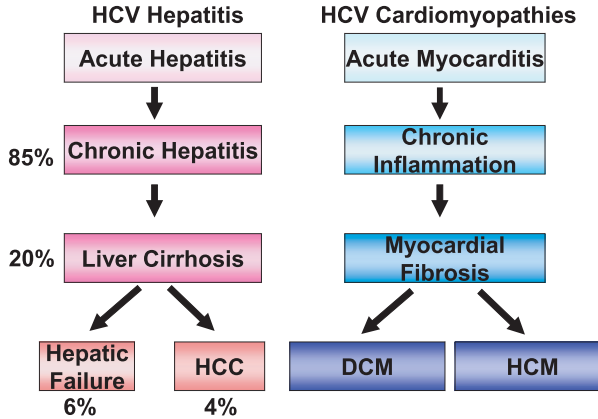

Fig. 6. Comparison of the pathogenesis of HCV hepatitis and cardiomyopathies

this patient was related to HCV infection. We have now treated another patient with HCV cardiomyopathy with interferon, and HCV RNA and cardiac troponin T both fell concomitantly during treatment (Fig. 5, right).

Pathogenesis of HCV hepatitis and cardiomyopathies is compared in Fig. 6. In HCV hepatitis, most patients develop chronic hepatitis, and years later liver cirrhosis, hepatic failure and hepatocellular carcinoma. In HCV heart diseases, most patients may develop chronic inflammation in the heart, and later dilated cardiomyopathy due to necrosis and loss of myocytes. However, myocytes in adult heart may not replicate. Proliferative stimuli induced by HCV infection may develop into myocyte hypertrophy and hypertrophic cardiomyopathy.

We are proposing collaborative work on a global network on myocarditis/cardiomyopathies to clarify the prevalence of cardiac involvement in HCV infection, and to perform treatment trials.

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