Hepatitis C virus infection in inclusion body myositis

A case-control study

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ABSTRACT

Objective: To clarify whether there is any association between inclusion body myositis (IBM) and hepatitis C virus (HCV) infection.

Methods: We assessed the prevalence of HCV infection in 114 patients with IBM whose muscle biopsies were analyzed pathologically for diagnostic purpose from 2002 to 2012 and in 44 age-matched patients with polymyositis diagnosed in the same period as a control by administering a questionnaire survey to the physicians in charge. We also compared clinicopathologic features including the duration from onset to development of representative symptoms of IBM and the extent of representative pathologic changes between patients with IBM with and without HCV infection.

Results: A significantly higher number of patients with IBM (28%) had anti-HCV antibodies as compared with patients with polymyositis (4.5%; odds ratio 8.2, 95% confidence interval 1.9–36) and the general Japanese population in their 60s (3.4%). Furthermore, between patients with IBM with and without HCV infection, we did not find any significant difference in the clinicopathologic features, indicating that the 2 groups have essentially the same disease regardless of HCV infection.

Conclusion: Our results provide the statistical evidence for an association between IBM and HCV infection, suggesting a possible pathomechanistic link between the 2 conditions. *Neurology*® 2016;86:211–217

GLOSSARY

Ab = antibodies; **CI** = confidence interval; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HTLV-1** = human T-lymphotropic virus type 1; **IBM** = inclusion body myositis; **IFN** = interferon; **MHC** = major histocompatibility complex; **NCNP** = National Center of Neurology and Psychiatry; **OR** = odds ratio; **PM** = polymyositis.

Inclusion body myositis (IBM) is the most common form of idiopathic inflammatory myopathy among individuals aged over 50 years, and its pathomechanism is not fully understood.[1] While the influence of genetic backgrounds on disease susceptibility and clinical phenotype has been suggested,[2] environmental factors might be involved with the pathogenesis as well. For instance, our recent study has shown that the number of patients with IBM is increasing in Japan, suggesting that westernization of dietary habits may influence the occurrence of the disease.[3] To elucidate such environmental factors that can trigger IBM pathogenesis would lead to better understanding of the enigmatic pathomechanism.

Chronic infection with hepatitis C virus (HCV) in patients with IBM has been reported in several articles,[4–9] suggesting a possible association of HCV infection with IBM. Nevertheless, no statistical evidence for the association has been provided and it is not known whether any etiologic link exists between the 2 conditions or it is a coincidence. We therefore conducted a retrospective case-control study to clarify whether HCV infection is associated with IBM.

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METHODS **Epidemiologic analyses.** The National Center of Neurology and Psychiatry (NCNP) functions as a referral center for muscle pathology and collects muscle biopsy samples from all over Japan. We re-evaluated muscle biopsy samples collected at NCNP

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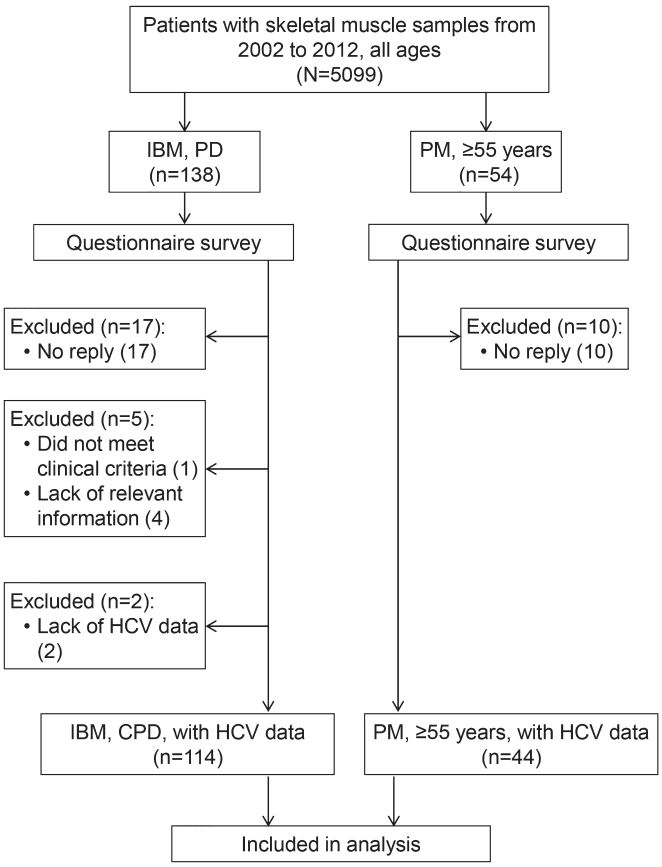
Figure 1 Study flow diagram



CPD = clinicopathologically defined; HCV = hepatitis C virus; IBM = inclusion body myositis; PD = pathologically defined; PM = polymyositis.

over 10 years from May 2002 to April 2012 and found 138 cases fulfilling pathologic criteria to define clinicopathologic IBM from the 2011 European Neuromuscular Centre (ENMC) IBM Research Diagnostic Criteria: (1) endomysial inflammatory infiltrate, (2) rimmed vacuoles (RV), and (3) aberrant protein accumulation (p62 or congophilic deposits) in muscle fibers.[10] We sent a questionnaire to the physicians in charge of the patients (appendix e-1 on the *Neurology*® Web site at Neurology.org) inquiring into (1) serum anti-HCV antibodies (Ab), hepatitis B virus (HBV) antigens (if any, the types of the antigens), anti-HIV Ab, and anti–human T-lymphotropic virus type 1 (HTLV-1) Ab; (2) distribution of affected muscles; (3) age at onset; and (4) duration from onset to the development of representative symptoms of IBM: (1) incapability of opening a plastic bottle, which reflects finger flexion weakness; (2) incapability of standing up from a squatting position, which reflects quadriceps femoris weakness; and (3) loss of ambulation. As a disease control, we also investigated 54 consecutive age-matched (>55 years old at muscle biopsy) patients with polymyositis (PM) whose muscle pathology was evaluated at NCNP in the same period and diagnosed as definite PM using the diagnostic criteria of Dalakas and Hohlfeld.[11]

We received replies from physicians of 121 patients with IBM and 44 patients with PM. Among the patients with IBM, the following 7 patients were excluded from further study: (1) one patient whose age at onset was 42 years, not fulfilling the ENMC criteria; (2) 4 patients whose relevant clinical information was lacking and thus we could not judge whether they met the clinical criteria; and (3) 2 patients who did not receive a test for anti-HCV Ab. Consequently, we analyzed 114 patients with IBM who met criteria for clinicopathologically defined IBM in the ENMC criteria and 44 age-matched patients with PM (mean ages at muscle biopsy were 69.0 ± 7.9 years and 69.0 ± 7.5 years, respectively) (figure 1).

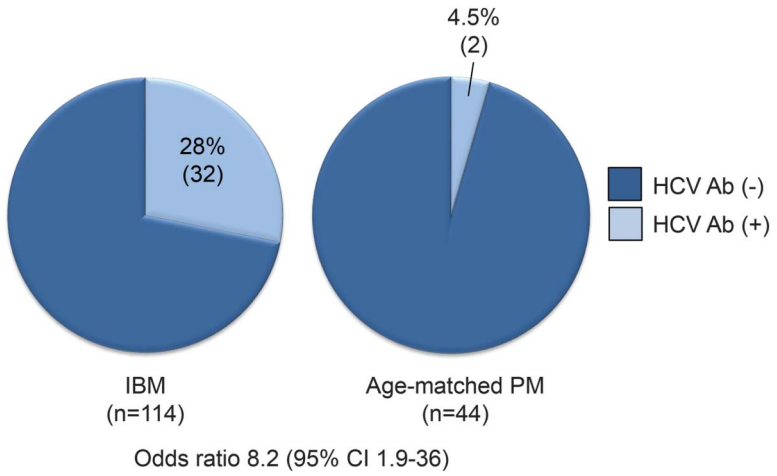
Pathologic analyses. Frequencies of fibers with RV, which is known as a pathologic hallmark of IBM, were assessed in more than 300 fibers on frozen muscle sections stained for modified Gomori trichrome. Major histocompatibility complex (MHC) class 1 and 2 expressions in muscle fibers are often seen in idiopathic inflammatory myopathies including IBM.[12] We performed immunohistochemical analyses for class 1 and 2 using 6-μm-thick frozen sections and monoclonal Ab (HLA-ABC, W6/32, 1:5,000 dilution, Thermo Fisher Scientific, Waltham, MA; and HLA-DR, B308, 1:5,000, Affinity BioReagents, Golden, CO) with the Ventana immunohistochemistry detection system (Ventana Medical Systems, Tucson, AZ). We assessed proportions of cases with a particular staining pattern of MHC 1 and 2: expression of MHC class 1 and 2 was graded as follows: − meant no positively stained fibers, and 1+, 2+, 3+, and 4+ were defined according to frequency of positively stained fibers, corresponding to 1%–10%, 11%–25%, 26%–50%, and 51%–100%, respectively. We judged as positive only when the cytoplasm of non-necrotic fibers was diffusely stained and negative if only sarcolemma were stained.

For immunohistochemical analyses of HCV peptides, we prepared 7-μm-thick frozen sections and fixed them as described previously.[13] The primary antibodies were as follows: HCV-core (C7-50; 1:500; Thermo Fisher Scientific), HCV-NS1 (polyclonal; 1:500; Abbiotec, San Diego, CA), HCV-NS5a (7-D4; 1:500; Virogen, Watertown, MA), CD68 (H-255; 1:200; Santa Cruz Biotechnology, Dallas, TX), and dystrophin (Dy8/6C5; 1:200; Novocastra Laboratories, Newcastle upon Tyne, UK). We labeled the antibodies with fluorophores by using APEX Antibody Labelling Kits (Invitrogen, Carlsbad, CA) according to the manufacturer's instruction. The antibodies for HCV-core, -NS1, and -NS5a were labeled with the same fluorophore. After 2-hour incubation at room temperature, we observed the specimens with BZ-X710 fluorescence microscope (Keyence, Osaka, Japan).

RT-PCR for HCV-RNA. RNA was extracted from frozen skeletal muscle using PureLink RNA Mini Kit (Life Technologies, Gaithersburg, MD) and reverse transcribed into cDNA with SuperScript VILO cDNA synthesis Kit (Life Technologies). We amplified 260-bp products of the cDNA to verify the presence of HCV-RNA, using the following primers, which had been developed to detect HCV-RNA in liver and serum: sense, 5′ GCC ATG GCG TTA GTA TGA GT 3′, and antisense, 5′ TGC ACG GTC TAC GAG ACC TC 3′.[14] Control muscle samples were derived from subjects with anti-HCV Ab, whose clinicopathologic diagnoses were PM (n = 3), acquired necrotizing myopathies (n = 3), mitochondrial diseases (n = 3), neuropathies (n = 3), myofibrillar myopathies (n = 2), Becker muscular dystrophy (n = 1), primary amyloidosis (n = 1), polymyalgia rheumatica (n = 1), and normal or nonspecific pathologies (n = 4).

Statistical analyses. All statistical analyses were performed using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). We used Fisher exact test to compare qualitative variables, parametric unpaired *t* test and nonparametric Mann-Whitney tests to compare continuous variables, Kaplan-Meyer curves and Gehan-Breslow-Wilcoxon test to compare the speed of development of symptoms, and χ^2 test for trend to estimate the relationship between patterns of staining of MHC class 1 or 2 and presence of HCV infection. We considered p values <0.05 statistically significant.

Figure 2 Prevalence of HCV infection



Positive rates of anti-hepatitis C virus antibodies (HCV Ab) in the inclusion body myositis (IBM) and polymyositis (PM) groups are shown. The numbers of positive subjects are shown inside parentheses. CI = confidence interval.

Standard protocol approvals, registrations, and patient consents. The study was approved by the NCNP Ethical Committee (A2013-003). All patients gave written informed consents for the use of materials for neuromuscular research.

RESULTS **High prevalence of HCV infection in patients with IBM.** We found that 32 (28%) out of 114 patients with IBM had anti-HCV Ab (figure 2). This prevalence was significantly higher than the age-matched PM group (2/44 [4.5%]).

In contrast, positive rates of anti-HTLV-1 Ab, anti-HIV Ab, and HBV antigens did not show significant differences between the IBM and PM groups. Positive rates of anti-HTLV-1 Ab were 7.8% (4/51) in the IBM group and 25% (4/16) in the PM group (odds ratio [OR] 0.26, 95% confidence interval [CI] 0.056–1.2). None had anti-HIV Ab in our cohort (data were available in 44 patients with IBM and 14 patients with PM). HBV antigens were positive in 1.8% (2/109) of the patients with IBM and 2.3%

Table 1 Clinical and pathologic features of the patients with inclusion body myositis

	Anti-HCV Ab		
	Positive	Negative	*p* Value
Male:female	1.3:1	1.4:1	0.84
Age at onset, y, mean ± SD	65.7 ± 7.8	64.1 ± 8.6	0.37
Concurrent autoimmune disease, % (n)[a]	11 (3/28)	18 (13/72)	0.55
Serum CK level, IU/L, median (range)	455 (84–3,085)	487 (75–2,400)	0.43
Positive ANA, % (n)	26 (7/27)	29 (21/72)	0.81
Positive anti-SS-A Ab, % (n)	16 (4/25)	15 (8/52)	1.00
Positive anti-SS-B Ab, % (n)	4 (1/24)	6 (3/52)	1.00
Frequency of fibers with RV, % (range)[b]	1.6 (0.2–8.1)	2.3 (0.2–14)	0.24
Pattern of staining of MHC class 1, % (n)[c]			0.92
–	0	0	
1+	6 (2/32)	10 (8/82)	
2+	34 (11/32)	28 (23/82)	
3+	25 (8/32)	29 (24/82)	
4+	34 (11/32)	33 (27/82)	
Pattern of staining of MHC class 2, % (n)[c]			0.85
–	6 (2/32)	15 (12/82)	
1+	38 (12/32)	33 (27/82)	
2+	38 (12/32)	27 (22/82)	
3+	13 (4/32)	18 (15/82)	
4+	6 (2/32)	7 (6/82)	

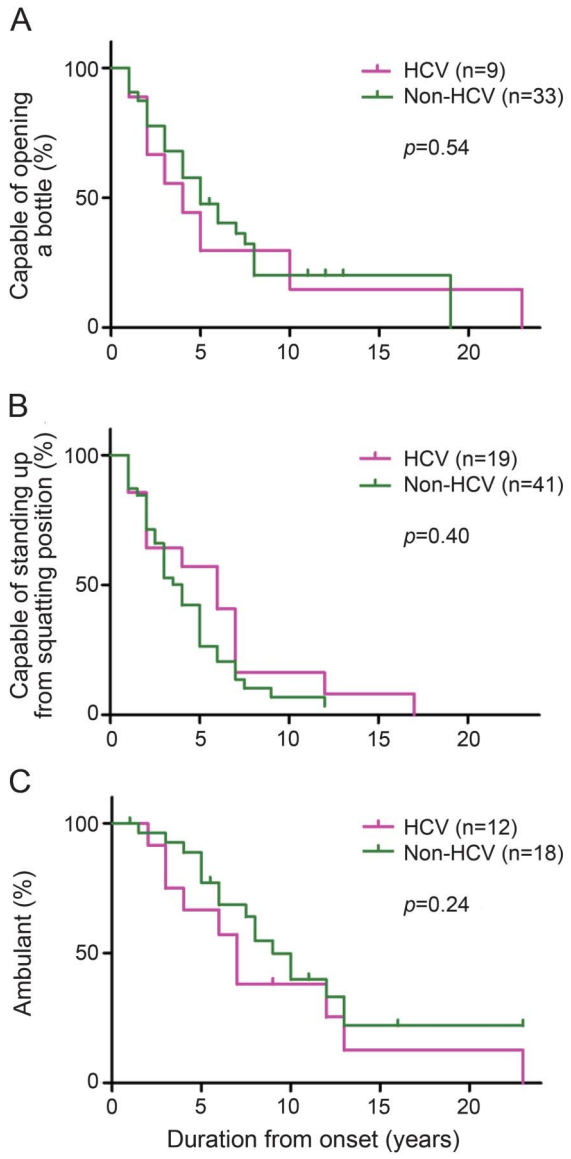
Abbreviations: Ab = antibodies; ANA = antinuclear antibodies; CK = creatine kinase; HCV = hepatitis C virus; MHC = major histocompatibility complex; RV = rimmed vacuoles.

[a] In the 3 anti-HCV Ab-positive patients who had autoimmune diseases, 2 had autoimmune thyroid disease (Hashimoto thyroiditis) and one had Sjögren syndrome. In the 13 negative patients, the following diseases were described: autoimmune thyroid disease (n = 5: Hashimoto thyroiditis, n = 3, and Graves disease, n = 2), Sjögren syndrome (n = 5), primary biliary cirrhosis (n = 2), rheumatoid arthritis (n = 2), autoimmune hepatitis (n = 1), and idiopathic thrombocytopenic purpura (n = 1). Four of the negative patients had multiple autoimmune diseases.

[b] Cases with more than 300 muscle fibers were analyzed. The number of anti-HCV Ab-positive patients analyzed was 31 and that of negative ones was 74.

[c] – to 4+ = see Methods.

Figure 3 Development of symptoms



Kaplan-Meier curves to compare the durations from onset to each following status of patients with inclusion body myositis with hepatitis C virus (HCV) with that of the patients without HCV infection (non-HCV): inability to open a plastic bottle (A), inability to stand up from squatting position (B), and loss of ambulation (C). Medians of the periods were 4 vs 5 years, 6 vs 4 years, and 7 vs 9 years, respectively.

(1/44) of the patients with PM (OR 0.80, 95% CI 0.071–9.1). Two patients with IBM had both anti-HCV and anti-HTLV-1 Ab, and one had both anti-HCV Ab and HBV antigens.

Clinical and pathologic features of patients with IBM with HCV infection. Sex ratio, age at onset, serum creatine kinase level, and frequency of concurrent autoimmune diseases and detection of autoantibodies (antinuclear antibodies, anti-SS-A antibodies, and anti-SS-B antibodies) showed no significant difference between the IBM groups with and without anti-HCV Ab (table 1). There were no significant differences in the speed of development of the disease (figure 3).

No significant differences were observed in terms of the frequency of fibers with RVs and the myofiber staining pattern on immunohistochemistry for MHC class 1 and 2 (table 1).

Individual data of each subject are described in appendix e-2.

HCV infection in patients with IBM. Information about the development of muscle symptom after treatment for HCV was available in 29 patients with IBM with anti-HCV Ab. Among them, 15 patients had received treatment for HCV prior to the onset of muscle symptoms, and the most common drug was interferon (IFN)–α (table e-1). Of particular interest, patient 9 developed the symptom of IBM during the first course of IFN-α treatment, and it was aggravated during the second course. Similarly, patient 32 manifested the initial muscle symptoms during treatment with IFN-α with ribavirin. None of the 26 patients whose relevant data were available showed improvement in muscle weakness after treatment for HCV infection.

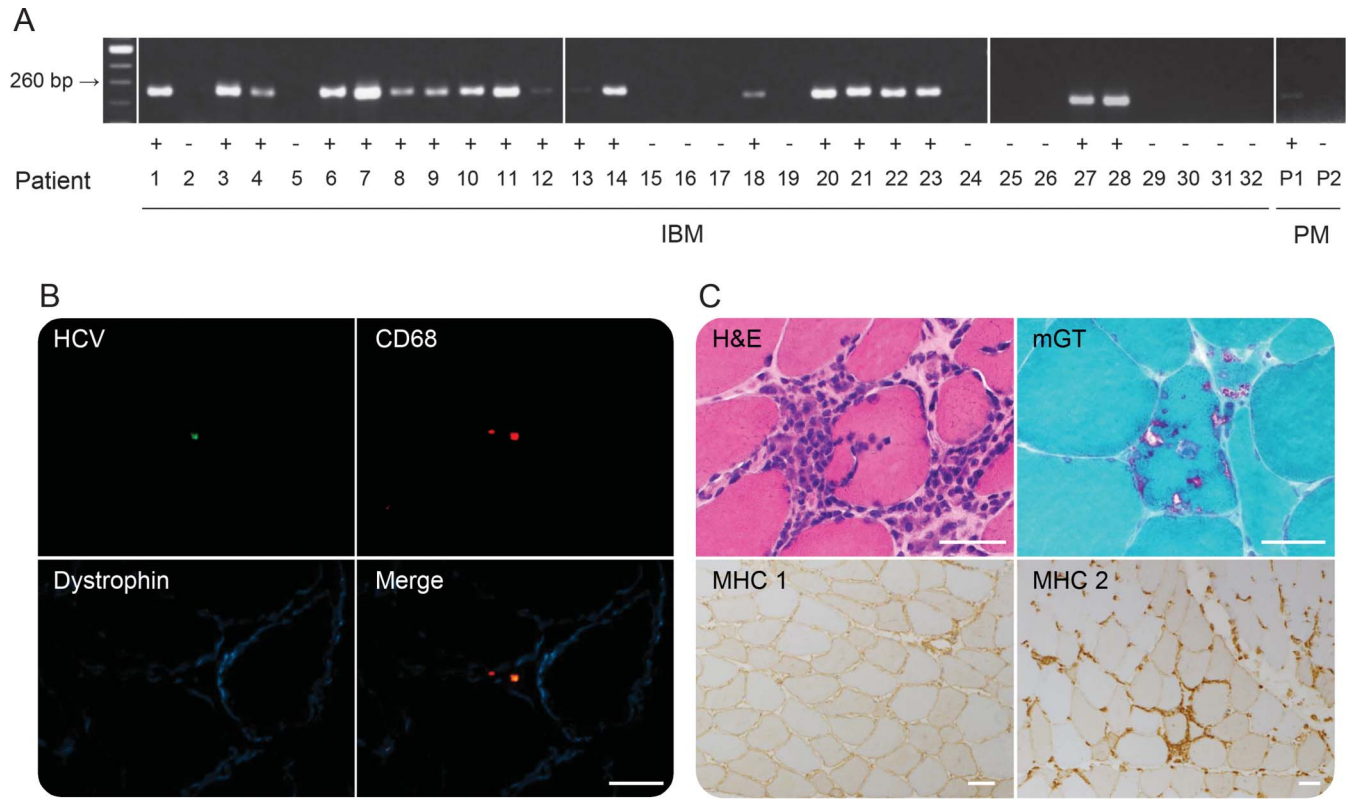
The data for genotype/serotype of the virus in serum were available in 11 patients: 7 had type 1 and 4 type 2 (table e-1).

RT-PCR for HCV-RNA in muscle tissues. HCV-RNA in the muscle specimens was detected in 19 (59%) of 32 patients with IBM with anti-HCV Ab (figure 4A). Meanwhile, HCV-RNA in muscle was found in 20 (95%) of 21 patients without IBM with anti-HCV Ab ($p = 0.0040$). In one of the 2 patients with PM with anti-HCV Ab, HCV-RNA was detected.

Immunohistochemistry for HCV peptide. To confirm the localization of HCV in muscles, we performed immunohistochemistry against HCV peptides. HCV peptides were detected in endomysium, mostly being localized within macrophages (figure 4B), but never within muscle fibers or T cells (not shown).

DISCUSSION Our study demonstrated significantly higher prevalence of HCV infection in the IBM cohort (28%) compared to the age-matched PM cohort (4.5%). The prevalence of HCV infection in the general Japanese population in their 60s in 2000 was estimated to be 3.4%,[15] indicating that the prevalence among patients with PM is virtually the same as that of the general population, while that among patients with IBM is one digit higher. These facts demonstrate a clear association between IBM and HCV infection. Nevertheless, clinical progression and extent of pathologic findings were essentially identical between HCV-positive and -negative patients with IBM, suggesting that HCV infection is most likely not a key determinant factor to develop IBM but rather serves as one of the triggers. This notion is in fact compatible with the fact that anti-HCV Ab were

Figure 4 HCV in muscle tissues



(A) RT-PCR for hepatitis C virus (HCV)–RNA in frozen muscle samples from patients with inclusion body myositis (IBM) and patients with polymyositis (PM) with anti-HCV antibodies (Ab). The 260-bp bands correspond to HCV-RNA. (B) Representative pictures of immunohistochemistry for HCV peptides (patient 14). HCV peptides are localized within a CD68-positive macrophage. Scale bar denotes 20 μm. (C) Muscle pathology of IBM shows endomysial mononuclear cellular infiltration on hematoxylin & eosin stain (H&E), rimmed vacuoles on modified Gomori trichrome stain (mGT), and major histocompatibility complex (MHC) 1 and 2 expression in muscle fibers. Scale bars denote 20 μm in (B) and 50 μm in (C).

negative in 72% of patients with IBM in our cohort. Interestingly, several articles reported the development of IBM in patients with retroviral infections such as HTLV-1 and HIV,[16–20] raising a possibility that some kinds of virus infection can be a trigger for IBM, although further studies are necessary to be more conclusive.

HCV infection is associated with not only hepatic diseases but also extrahepatic, often autoimmune, diseases, including mixed cryoglobulinemia, Sjögren syndrome, autoimmune thyroid diseases, lymphoproliferative disorders, diabetes mellitus, renal diseases, porphyria cutanea tarda, and oral lichen planus.[21] In mixed cryoglobulinemia and B-cell non-Hodgkin lymphoma, capture of HCV viral particle by V_H1-69+ B1 cells and marginal-zone B cells and following B-cell clonal expansion is considered a main cause.[22] Although underlying pathomechanism is not well-established in the other conditions, HCV infection may potentially elicit immunogenicity in humans.[23]

Interestingly, HCV-RNA was much less often detected in muscles from patients with IBM with HCV infection compared to patients without IBM with HCV infection, although this should be interpreted carefully due to possible contamination of infected blood. One possible interpretation would be that the pathogen may have been cleared when autoimmune disease with insidious onset with considerable subclinical period, such as IBM, becomes clinically evident, although the virus plays some pathomechanistic roles such as bystander activation.[24] Alternatively, HCV infection may not be directly involved in the pathogenesis of IBM.

Focusing on the localization of HCV in muscle tissues, viral peptides were seen within endomysial macrophages, not within muscle fibers, as in the case of IBM with HTLV-1/HIV infection.[16] In IBM with HTLV-1/HIV infection, viral-positive endomysial macrophages are considered to possibly facilitate the autoimmune process by secreting proinflammatory cytokines.[17]

Notably, 2 patients developed IBM during treatment for HCV infection (the only common drug was IFN-α). In addition, one case report described a patient with IBM with a similar clinical course.[8] Type I IFNs have potential to stimulate autoreactive memory B cells, leading to their differentiation into autoreactive plasmablasts and subsequent increased production of autoantibodies.[25] Therefore, type I

IFNs are considered to be associated with amplification of autoimmunity in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.[25] Interestingly, during the last decade, several studies have identified B-cell signatures in IBM pathogenesis, including the discovery of an autoantibody.[26,27] These facts may suggest that the use of IFN-α increased the risk for development or aggravation of IBM. However, the evidence is anecdotal and we cannot conclude an association between IFN-α therapy and IBM. Further studies are necessary to elucidate this issue.

The proportion of genotype/serotype of HCV in our IBM cohort would be equivalent to that of the general Japanese population: genotypes 1 and 2 are 70% and 30%, respectively.[28] Implication of a specific type of the virus with IBM pathogenesis seems less likely, although the available data were limited.

While there was no significant difference between the groups of IBM and PM, the prevalence of HTLV-1 infection in each group is higher than in the general population, although the prevalence in the PM group was obtained from a limited number of subjects (the prevalence in general Japanese people aged 60–64 years in 2006–2007 was estimated to be 1.5% in men and 1.7% in women).[29] Our results may be supportive of the theory that HTLV-1 infection is associated with both IBM and PM.[17,30]

While there has been controversy about diagnostic criteria for IBM,[1,31] the 2011 ENMC IBM Research Diagnostic Criteria were established under consensus of experts highly experienced in dealing with IBM.[10] They require all the positive pathologic findings to categorize a patient with clinicopathologically defined IBM.[10] However, analysis for aberrant protein accumulation and electromicroscopic observation would not be performed frequently in clinical practice except for specialized institutes. Notably in this study, all 138 patients with endomysial inflammatory infiltrate, which we judged as positive only when mononuclear cells surrounded and occasionally invaded non-necrotic fibers (figure 4C), and RV showed cytoplasmic accumulation of aberrant protein (p62 was detected in all). Furthermore, all 116 patients whose relevant clinical information was provided fulfilled clinical features for clinicopathologically defined IBM in the criteria except for one patient who was slightly younger than the age limit, suggesting that the presence of the strictly judged endomysial inflammatory cell infiltration and RV may be enough to make a diagnosis of IBM.

We are aware of a few limitations to this study. First, there may be a selection bias. We could not receive replies of the questionnaire survey from the physicians who saw 17 of 138 patients with IBM pathology. Physicians who have encountered a patient with IBM with HCV infection may have tended to reply more willingly, resulting in overestimation of the prevalence of HCV infection, although even if all of the no-reply cases were IBM without HCV infection, the prevalence (24.4% [32/131]) would be significantly higher than the control (OR 6.8, 95% CI 1.6–30). Second, in order to make a genuine IBM cohort, we applied the ENMC criteria strictly. While the criteria possess a high specificity, sensitivity is not high.[31] Thus, we cannot exclude a possibility that we may have missed patients with IBM lacking typical clinicopathologic features, which would affect the prevalence calculation. Finally, this study was performed only in a single cohort in one country while the prevalence of HCV infection and the prevailing genotype differ among different countries or regions. Therefore, there remains a possibility that this phenomenon may be unique to the Japanese population. Validation should be performed in several independent cohorts from different countries.

We have demonstrated that HCV infection is associated with IBM in a large Japanese cohort. Our results raise a possibility of a pathomechanistic link between the 2 conditions although further studies are necessary.

AUTHOR CONTRIBUTIONS

A.U. was involved in the conceptualization and design of the study, data analysis and interpretation, literature review, and drafting the manuscript. S.N., Y.K.H., R.S.T., and T.Y. were involved in technical or material support, data interpretation, and manuscript revision for intellectual content. I. Nonaka was involved in the supervision of pathologic analysis and manuscript revision for intellectual content. I. Nishino was involved in the supervision of all aspects including study design and data analysis and interpretation, and manuscript revision for intellectual content.

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DISCLOSURE

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REFERENCES

1. Benveniste O, Stenzel W, Hilton-Jones D, et al. Amyloid deposits and inflammatory infiltrates in sporadic inclusion body myositis: the inflammatory egg comes before the degenerative chicken. Acta Neuropathol 2015;129:611–624.

2. Mastaglia FL, Needham M. Inclusion body myositis: a review of clinical and genetic aspects, diagnostic criteria and therapeutic approaches. J Clin Neurosci 2015;22:6–13.
3. Suzuki N, Aoki M, Mori-Yoshimura M, et al. Increase in number of sporadic inclusion body myositis (sIBM) in Japan. J Neurol 2012;259:554–556.
4. Alexander JA, Huebner CJ. Hepatitis C and inclusion body myositis. Am J Gastroenterol 1996;91:1845–1847.
5. Kase S, Shiota G, Fujii Y, et al. Inclusion body myositis associated with hepatitis C virus infection. Liver 2001;21:357–360.
6. Tsuruta Y, Yamada T, Yoshimura T, et al. Inclusion body myositis associated with hepatitis C virus infection. Fukuoka Igaku Zasshi 2001;92:370–376.
7. Yakushiji Y, Satoh J, Yukitake M, et al. Interferon beta-responsive inclusion body myositis in a hepatitis C virus carrier. Neurology 2004;63:587–588.
8. Warabi Y, Matsubara S, Mizutani T, et al. Inclusion body myositis after interferon-alpha treatment in a patient with HCV and HTLV-1 infection [in Japanese]. Rinsho Shinkeigaku 2004;44:609–614.
9. Alverne AR, Marie SK, Levy-Neto M, et al. Inclusion body myositis: series of 30 cases from a Brazilian tertiary center [in Portuguese]. Acta Rheumatol Port 2013;38:179–185.
10. Rose MR; ENMC IBM Working Group. 188th ENMC International Workshop: inclusion body myositis, 2–4 December 2011, Naarden, the Netherlands. Neuromuscul Disord 2013;23:1044–1055.
11. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet 2003;362:971–982.
12. Rodríguez Cruz PM, Luo YB, Miller J, et al. An analysis of the sensitivity and specificity of MHC-I and MHC-II immunohistochemical staining in muscle biopsies for the diagnosis of inflammatory myopathies. Neuromuscul Disord 2014;24:1025–1035.
13. Malicdan MC, Noguchi S, Nishino I. Monitoring autophagy in muscle diseases. Methods Enzymol 2009; 453:379–396.
14. Walker FM, Dazza MC, Dauge MC, et al. Detection and localization by in situ molecular biology techniques and immunohistochemistry of hepatitis C virus in livers of chronically infected patients. J Histochem Cytochem 1998;46:653–660.
15. Tanaka J, Kumagai J, Katayama K, et al. Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995–2000. Intervirology 2004;47:32–40.
16. Cupler EJ, Leon-Monzon M, Miller J, et al. Inclusion body myositis in HIV-1 and HTLV-1 infected patients. Brain 1996;119:1887–1893.
17. Dalakas MC. Inflammatory, immune, and viral aspects of inclusion-body myositis. Neurology 2006;66(2 suppl 1): S33–S38.
18. Dalakas MC, Rakocevic G, Shatunov A, Goldfarb L, Raju R, Salajegheh M. Inclusion body myositis with human immunodeficiency virus infection: four cases with clonal expansion of viral-specific T cells. Ann Neurol 2007;61:466–475.
19. Ozden S, Gessain A, Gout O, et al. Sporadic inclusion body myositis in a patient with human T cell leukemia virus type 1-associated myelopathy. Clin Infect Dis 2001; 32:510–514.
20. Matsuura E, Umehara F, Nose H, et al. Inclusion body myositis associated with human T-lymphotropic virus-type I infection: eleven patients from an endemic area in Japan. J Neuropathol Exp Neurol 2008;67:41–49.
21. Galossi A, Guarisco R, Bellis L, Puoti C. Extrahepatic manifestations of chronic HCV infection. J Gastrointestin Liver Dis 2007;16:65–73.
22. Dammacco F, Sansonno D. Therapy for hepatitis C virus-related cryoglobulinemic vasculitis. N Engl J Med 2013; 369:1035–1045.
23. Zampino R, Marrone A, Restivo L, et al. Chronic HCV infection and inflammation: clinical impact on hepatic and extra-hepatic manifestations. World J Hepatol 2013;5: 528–540.
24. Münz C, Lünemann JD, Getts MT, et al. Antiviral immune responses: triggers of or triggered by autoimmunity? Nat Rev Immunol 2009;9:246–258.
25. Hiepe F, Dörner T, Hauser AE, et al. Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. Nat Rev Rheumatol 2011;7:170–178.
26. Pluk H, van Hoeve BJ, van Dooren SH, et al. Autoantibodies to cytosolic 5′-nucleotidase 1A in inclusion body myositis. Ann Neurol 2013;73:397–407.
27. Larman HB, Salajegheh M, Nazareno R, et al. Cytosolic 5′-nucleotidase 1A autoimmunity in sporadic inclusion body myositis. Ann Neurol 2013;73:408–418.
28. Wu S, Kanda T, Nakamoto S, et al. Prevalence of hepatitis C virus subgenotypes 1a and 1b in Japanese patients: ultra-deep sequencing analysis of HCV NS5B genotype-specific region. PLoS One 2013;8:e73615.
29. Ministry of Health, Labor and Welfare, Japan. Present Situation and Measure on HTLV-1 [in Japanese]. Available at: http://www.google.co.jp/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CB8QFjAA&url=http%3A%2F%2Fwww.kantei.go.jp%2Fjp%2Fsingi%2Fhtlv%2Fdai1%2Fgenjoutotaisaku.pdf&;ei=k7wLVfOTGYih8QXkyYE4&usg=AFQjCNHI9ZlSte2X-4gha7X4w9ImExasWg&sig2=Ut8RUL_hqKk8WB5aVaAXmg&bvm=bv.88528373,d.dGc. Accessed March 27, 2015.
30. Desdouits M, Cassar O, Maisonobe T, et al. HTLV-1-associated inflammatory myopathies: low proviral load and moderate inflammation in 13 patients from West Indies and West Africa. J Clin Virol 2013;57:70–76.
31. Lloyd TE, Mammen AL, Amato AA, et al. Evaluation and construction of diagnostic criteria for inclusion body myositis. Neurology 2014;83:426–433.