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【 CASE REPORT 】

# A Patient with HCV Infection and a Sustained Virological Response to Direct-acting Antiviral Treatment Who Developed Inclusion Body Myositis

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**Abstract:**
We report the case of a 75-year-old woman who was found to have hepatitis C virus (HCV) infection in 1987. Before treatment in 2016, she was found to have mixed cryoglobulinemia (MC). Direct-acting antiviral (DAA) treatment produced a sustained virological response 12 (SVR12). She noticed gradual muscle weakness in 2015 and the gradual development of dysarthria and dysphagia in 2017. We performed a muscle biopsy that showed inclusion body myositis (IBM). To the best of our knowledge, this is first case of a patient with HCV infection, MC, and IBM, in which MC and IBM did not improve after an SVR12 was obtained by DAA treatment.

**Key words:** hepatitis C virus, inclusion body myositis, direct-acting antiviral, mixed cryoglobulinemia, sustained virological response

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## Introduction

The recent introduction of direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C infection has led to a dramatic improvement in the cure rate (1). Inclusion body myositis (IBM) is a chronic progressive muscle disorder that affects individuals of >50 years of age (2). The myositis is histologically characterized by lymphocytic inflammation and autophagic vacuoles called rimmed vacuoles (3). Previous studies have suggested that hepatitis C virus (HCV) infection is associated with inflammatory myopathy (4). However, there are no reports on an association between IBM and the eradication of HCV by DAA therapy. To the best of our knowledge, this is the first report of an HCV-infected patient, who developed IBM and mixed cryoglobulinemia (MC), and who was also treated with DAAs. We herein report this rare case and present a review of the literature.

## Case Report

A 75-year-old woman was hospitalized in 2017 because of gradually worsening generalized muscle weakness in her thighs, wrists, and fingers that had begun in 2015. In 2017, she also developed dysarthria and dysphagia.

The patient had received a blood transfusion at 37 years of age during surgery (complete hysterectomy). She had a medical history of hypertension and surgery for primary colon cancer. She received the diagnosis of MC when she underwent laboratory testing before starting DAA therapy; however, she had no symptoms of cryoglobulinemia. She did not abuse alcohol and did not smoke cigarettes. Her family history was unremarkable, and her only regular medication was a calcium antagonist, which was used to treat hypertension.

She had been diagnosed with HCV infection in 1987. In 2002, she underwent therapy with interferon (IFN) plus

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**Table. The Laboratory Data before and after the Patient Obtained a Sustained Virological Response with Direct Active Antiviral Therapy.**

| Variables | Pretreatment | SVR12 | Muscle biopsy | 6 months after muscle biopsy |
|---|---|---|---|---|
| TP(g/dL) | 9.1 | 8.5 | 8.9 | 8.6 |
| Alb(g/dL) | 3.4 | 3.4 | 3.8 | 3.9 |
| AST(IU/L) | 136 | 61 | 56 | 53 |
| ALT(IU/L) | 107 | 53 | 57 | 37 |
| CK(IU/L) | 1,366 | 1,634 | 1,544 | 1,711 |
| IgG(mg/dL) | 3,256 | 3,198 | 2,724 | 2,786 |
| IgM(mg/dL) | 418 | 830 | 771 | 697 |
| HCV-RNA(Log IU/mL) | 6.5 | undetectable | undetectable | undetectable |

The data show the laboratory data obtained before treatment, at the achievement of an SVR12, and the results of the muscle biopsy during admission. TP: Total Protein, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, CK: Creatine Kinase, IgG: Immunoglobulin G, IgM: Immunoglobulin M

ribavirin for 24 weeks; however, HCV eradication was not obtained. She then received hepatoprotective therapy with glycyrrhizic acid. In 2016, she was referred to our institution and has been followed for chronic hepatitis C (genotype1b, IL28B polymorphisms TG). IFN-free antiviral treatment consisting of ombitasvir/paritaprevir/ritonavir was initiated in May 2016 after the patient was confirmed to harbor the NS5A-Y93 wild-type virus. Treatment was continued for 12 weeks. Table shows the results of laboratory testing before the initiation of DAA and after the cessation of DAA treatment. HCV RNA could not be detected at 5 weeks after the start of DAA treatment, and remained undetectable at 12 weeks after completion of therapy [sustained virological response 12 (SVR12)] (Table, Fig. 1).

A general physical examination upon the patient's hospital admission in 2017 did not reveal any abnormalities other than forearm muscle atrophy. Her right and left hand grasping power were 4 kg and 10 kg, respectively. A neurologic examination revealed facial and extremity muscle weakness. She was unable to stand or remain standing. Manual muscle testing (MMT) revealed scores ranging from 5 (normal) to 0 (complete paralysis). The noteworthy scores were as follows: (right/left) deltoids (4/4), triceps (5/4), hamstrings (4/4), and quadriceps femoris (5/4) (Fig. 1).

The laboratory results upon her 2017 hospital admission for muscle weakness, dysarthria, and dyspahgia included the following: aspartate aminotransferase, 56 IU/L; alanine aminotransferase, 57 IU/L; and creatine kinase (CK), 1,544 IU/L. Hepatitis B virus surface antigen and HCV RNA were undetectable, and the patient's tumor marker levels were almost normal. Tests for antinuclear antibodies, antinuclear ribonucleoprotein antibodies, anti-mi 2 antibodies, aldolase, and anti-human immunodeficiency virus antigen antibodies were all negative (Table).

B-mode ultrasonography of the abdomen revealed that edge was dull, the surface was irregular and the absence of any obvious space-occupying lesions. The mean stiffness of the liver was 29.1 and 11.9 kPa on fibroscan and shear wave elastography, respectively, indicating the absence of HCC and cirrhosis.

Plain computerized tomography (CT) of the abdomen revealed symmetrical atrophy of both forearms, and MRI revealed a symmetrical heterogeneous high signal of both thighs on T2- short tau inversion recovery (STIR) sequences (Fig. 2).

Upon initiation of DAA therapy in 2016, the patient's CK level was 938 IU/L. The patient noticed dysarthria before her 2017 admission, and consulted a neurologist. Cranial CT was negative for intracranial lesions and extrapyramidal abnormalities. During DAA therapy, the patient's CK level gradually increased and peaked at 1,921 IU/L at week 12 of therapy (Fig. 1). The CK level ranged from 1,500 to 1,700 IU/L during outpatient monitoring. Upon admission in 2017, the patient's CK level was 1,544 IU/L, and she had difficulty walking, talking, and swallowing. We suspected polymyositis/dermatomyositis, and she consulted a neurologist.

A muscle biopsy of the right rectus femoris was performed. The histopathological examination revealed CD8-positive inflammatory cell infiltration with non-necrotic muscle fibers. Rimmed vacuoles were present in some muscle fibers. The specimen was immunopositive for p62 (5). Based on these clinical laboratory findings, the patient was diagnosed with IBM (Fig. 3).

## Discussion

HCV infection is not only associated with hepatic diseases but also with extrahepatic diseases, often including autoimmune diseases such as MC, myositis, Sjögren's syndrome, autoimmune thyroid diseases, lymphoproliferative disorders, diabetes mellitus, and renal diseases (4). We report a very rare and informative case of a patient with HCV infection who was treated by DAA who developed IBM and MC. To our knowledge, no cases with these 2 manifestations have been reported. Notably, this is the first case report of a patient who achieved HCV eradication and an SVR12 after DAA therapy, with no improvement in IBM or MC.

Previous studies have suggested a relationship between HCV infection and inflammatory myopathy (3, 6). A recent

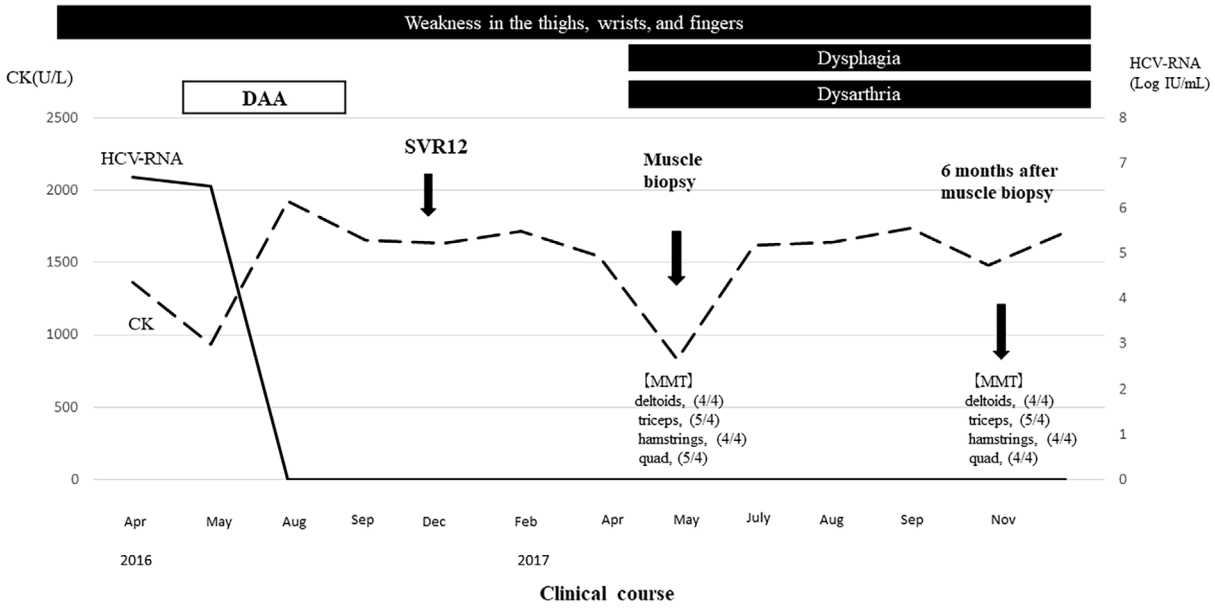


**Figure 1.** **The clinical course of one case. The clinical course of a patient who obtained HCV eradication and an SVR12 through DAA therapy without an improvement of IBM and MC. CK: creatine kinase, HCV: hepatitis C virus, DAA: direct acting antiviral, IBM: inclusion body myositis, MC: mixed cryoglobulinemia, SVR12: sustained virological response 12, MMT: manual muscle testing**

study revealed a significantly higher prevalence of HCV infection in a cohort of patients with IBM (28%), in comparison to an aged-matched cohort of patients with polymyositis (4.5%) (7). Although chronic viral infections are thought to act as a trigger in the pathogenesis of IBM, the etiology of IBM remains unknown (6, 7).

IFN has been used successfully to treat patients with HCV infection, and has improved the disease course of a patient with HCV-associated myopathy (8). On the other hand, another study suggested that the use of IFN-α increased the risk of the development or aggravation of IBM. IFN has the potential to stimulate autoreactive memory B cells, leading to their differentiation into autoreactive plasmablasts and a subsequent increase in the production of autoantibodies. Thus, IFN is considered to be associated with the amplification of autoimmunity in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (7). The association between HCV eradication by IFN-α therapy and IBM is therefore controversial.

DAAs are currently highly effective and safe for the eradication of HCV. Although our patient received DAA for the treatment of HCV infection and obtained HCV eradication, her muscle weakness did not improve and her CK level tended to increase. The association between HCV eradication as a result of DAA therapy and IBM is also unclear. Further studies should be performed to investigate the relationships between HCV infection and IBM.

The diagnosis of IBM is sometimes difficult (9), because we tend to assume that muscle weakness and atrophy occur as a result of aging or a variety of other conditions. The serum CK levels in IBM patients can be normal to mildly elevated and do not exceed 2,000 IU/L (10). In our patient, the CK levels were also <2,000 IU/L, both after the achievement of an SVR12 and during outpatient monitoring. If undiagnosed and untreated, many patients with IBM ultimately die of pneumonia due to the progression of extremity muscle weakness and dysphagia. Thus, the early diagnosis of IBM is important; a hepatologist who encounters a patient with HCV infection and slowly progressive muscle weakness or atrophy should be aware of the possibility of IBM.

MC is a highly prevalent extrahepatic disease that is most highly associated with HCV. The presence of HCV infection is estimated to account for up to 90% of MC cases (11). A previous study reported that when HCV is eradicated, the resolution or improvement of MC is almost always maintained (12)

The role of DAA therapy in the treatment of HCV-associated MC is not yet established; however, a growing body of evidence has emerged on the success of first-generation protease inhibitor therapy in combination with IFN or ribavirin (13). We must clarify the mechanisms involved in the improved outcomes of HCV-positive patients with MC as a result of DAA therapy. Studies on the treatment of MC with DAAs are underway.

Our case report is associated with a limitation in that the 12-week follow-up period after an SVR12 was achieved was too short to allow for the adequate assessment of the impact of treatment. Accordingly, long-term follow-up is required to assess the association between IBM and MC.

In conclusion, to the best of our knowledge, this is first case of a patient with HCV infection, MC, and IBM, in whom DAA treatment did not lead to the improvement of MC and IBM after the patient achieved an SVR12. This case report showed the treatment effects and limitations of

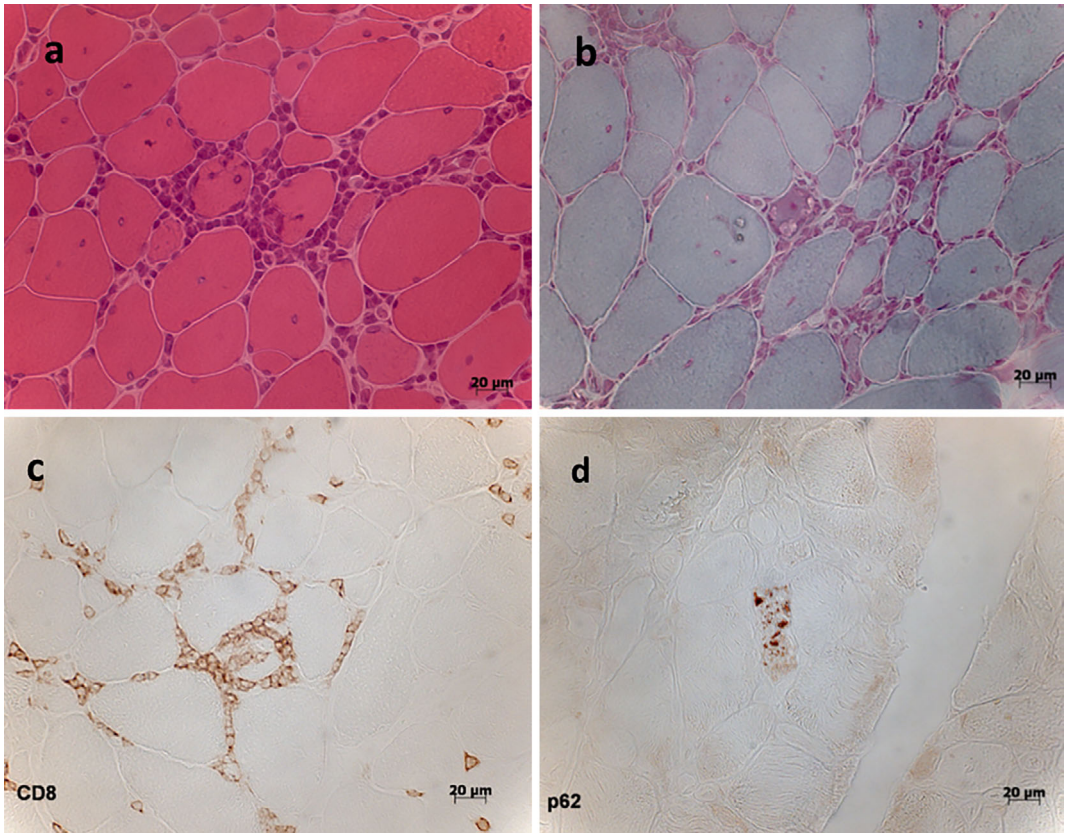


**Figure 2.** **The histological findings. A histopathological examination demonstrated CD8-positive inflammatory cell infiltration with non-necrotic muscular fibers. Rimmed vacuoles were present in some muscle fibers. The specimen was immunopositive for p62. Hematoxylin and Eosin staining (a), Gomori-Trichrome staining (b), immunohistochemical staining of anti-CD8 antibodies (c), immunohistochemical staining of anti-p62 antibodies (d).**

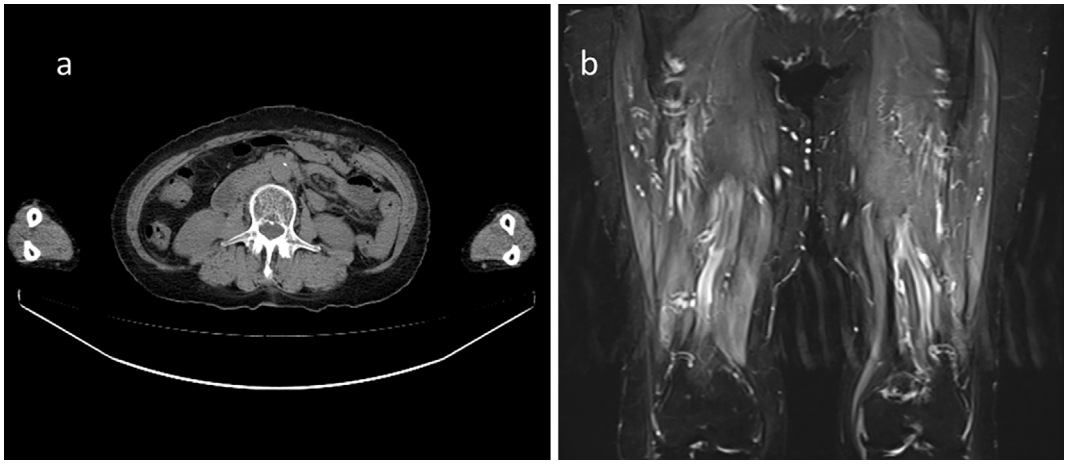


**Figure 3.** **The imaging findings. Plain CT in 2017 revealed symmetric atrophy of both forearms (a). MRI revealed symmetrical heterogeneous areas of high signal intensity in both thighs on T2-STIR sequences (b).**

new DAA treatments for extrahepatic diseases observed in patients with HCV infection. Further studies involving more patients are needed to investigate the association between HCV eradication and the progression of IBM.

**Author's disclosure of potential Conflicts of Interest (COI).**

Fumitaka Suzuki: Honoraria, Bristol-Myers Squibb. Yoshiyuki Suzuki: Honoraria, AbbVie. Kenji Ikeda: Honoraria, Dainippon Sumitomo Pharma and Eisai. Hiromitsu Kumada: Honoraria, MSD, Bristol-Myers Squibb, Gilead Sciences, AbbVie and Dainippon Sumitomo Pharma.

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