INTERNAL MEDICINE

□ CASE REPORT □

Rheumatoid Arthritis following a Treatment with IFN-alpha/Ribavirin against HCV Infection

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Abstract

We report a 48-year-old man who developed rheumatoid arthritis (RA) after a successful treatment with peg-IFN-alpha plus ribavirin for chronic hepatitis C virus (HCV) infection. He had a history of smoking and a single copy of the HLA-DRB1 shared epitope (SE). In a retrospective analysis, he exhibited the anti-CCP antibodies before the start of IFN plus ribavirin treatment. However, the titers of anti-CCP antibodies and BAFF levels were elevated by the IFN plus ribavirin therapy. These observations suggest that IFN plus ribavirin therapy may work as a "trigger" for RA in genetically and environmentally predisposed individuals by affecting the cytokine network.

Key words: anti-cyclic citrullinated peptide antibodies, B cell activating factor belonging to the TNF-family (BAFF), hepatitis C virus, interferon, ribavirin, rheumatoid arthritis, shared epitope

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Introduction

Autoimmune phenomena are not rare among patients with chronic hepatitis C virus (HCV) infection (1). Furthermore autoantibodies and autoimmune diseases can also develop during IFN-α treatment for HCV infection (2). Because of the biological properties of interferon, a large number of immune-related side effects have been reported (3). The combination of interferon (IFN) and ribavirin therapy has been used for the treatment of hepatitis C virus (HCV) infection. Although rheumatoid arthritis (RA) is one of the common autoimmune diseases, the development of RA after IFN plus ribavirin therapy, has been rarely reported (4, 5). We report the case of a man with HCV infection, in whom, HCV infection was precisely treated with INF-α and ribavirin. However, he developed RA after completion of this treatment.

Case Report

A 48-year-old Japanese man was diagnosed with HCV infection after abnormal liver function tests and HCV RNA was detected in 2007. There was no history of blood transfusion, however, he had a smoking history for 30 years. HCV RNA was detected at 6.3 Log IU/mL, genotype 2b, and liver biopsy showed chronic active hepatitis with pericellular fibrosis. Prior to therapy, there were no symptoms or signs suggesting rheumatic diseases, such as arthritis. He was started on combination treatment with peg-INF-α and ribavirin. This therapy was well tolerated for 24 weeks, when the HCV-RNA became negative and the anti-HCV treatment was completed. Two months after cessation of the INF-α and ribavirin treatment, the patient developed symmetrical polyarthritis with pain in the wrist and the metacarpophalangeal joints with prolonged morning stiffness. On physical examination, cardiovascular and respiratory examinations were unremarkable, and there was no sign

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Table 1. Laboratory Findings on Admission

Urinalysis	normal	**Serological tests**	
Peripheral blood		C-reactive protein	1.21mg/mL (<0.30)
Red blood cells	450×10^4/μL	Erythrocyte sedimentation rate	36mm/hr
Hemoglobin	12.7g/dL	IgG	2190mg/dL (900-2000)
Hematocrit	37.6%	C3	107mg/dL (70-120)
White blood cells	2700/μL	C4	14mg/dL (15-24)
Neutriphil	63.0%	Anti-nuclear Ab	×40 diffuse
Eosinophil	0%	Anti-ds DNA Ab	<10IU/mL (<10)
Monocyte	12.7%	Anti-CCP Ab	1720U/mL (<4.5)
Lymphocyte	24.3%	RF	16IU/mL (<20)
Platlet	9.1×10^4/μL	Cryoglobulin	negative
Prothrombin time	90.1%	Anti-RNP Ab	<5.0IU/mL (<5)
Blood chemistry		Anti-SSA Ab	<5.0IU/mL (<5)
Total protein	8.0g/dL	Anti-SSB Ab	<5.0IU/mL (<5)
Total bilirubin	0.8mg/dL	MMP-3	845ng/mL (<121)
Glutamic-oxaloacetic transaminase	28 IU/l (7-33)	HLA-DRB1	(*0405/0901)
Glutamic-pyruvic transaminase	17 IU/l (5-30)	**Virological test**	
Lactate dehydrogenase	241 IU/l (260-480)	HCV-Ab	13.99s/co (<0.99)
Alkaline phosphatase	217 IU/l (80-250)	HCV genotype	2b
Gamma-glutamyl transpeptidase	17 IU/l (5-55)	HCV-RNA	(-) LogIU/mL
Creatinine kinase	41 IU/l (60-160)	HCV-Ag	0.3fMol/L (<10)
Total cholesterol	170mg/dL		
Blood urea nitrogen	14.3mg/dL		
Creatinine	0.6mg/dL		

Abbreviation: RF; rheumatoid factor, Anti-CCP Ab; anti-cyclic citrullinated peptide antibody, MMP-3; matrix metalloproteinase-3, HCV; hepatitic C virus

of liver or spleen enlargement. There was swelling in the above-described joints. As shown in Table 1, laboratory data revealed a white blood cell count (WBC) 4,200 cells/mm^3, hemoglobin 11.8 g/dL, creatinine 0.5 mg/dL, aspartate aminotransferase 17 IU/mL, alanine aminotransferase 12 IU/mL, and alkaline phosphatase 84 UI. HCV-RNA was not detected in sera. C-reactive protein was 1.21 mg/dL and antinuclear antibody (ANA) was positive with a low titer (×80) and rheumatoid factor (RF) was negative. Anti-cyclic citrullinated peptide (CCP) antibodies were positive with a high titer (1,720 IU/mL). In HLA-DRB1 genotyping, he had a single copy of shared epitope (0405/0901). Although the X ray of the hand showed no remarkable finding, hand magnetic resonance imaging (MRI) detected bone erosions (Fig. 1), and the diagnosis of RA was made. He was initially treated with methotrexate (6 mg/week) combined with low dose sulfasalazine (1,000 mg/day) with a favorable response; decreased joint swelling and serum MMP-3 levels (Fig. 2).

Increased serum B cell activating factor belonging to the TNF-family (BAFF) has been observed in patients with HCV infection and elevated serum BAFF levels are associated with clinical features of autoimmunity suggesting that BAFF plays a role in HCV-related autoimmunity (6, 7). Therefore, we retrospectively assessed whether the serum BAFF levels and anti-CCP antibodies were modulated by IFN-α plus ribavirin therapy using frozen sera samples. As shown in Fig. 2, serum BAFF was markedly elevated after the start of the IFN plus ribavirin treatment. Although anti-CCP antibodies were detected before the IFN plus ribavirin treatment, the titers were gradually elevated parallel to the levels of BAFF following the anti-HCV treatment.

Discussion

It has become evident that HCV infection is associated with a variety of extra-hepatic rheumatic disorders, including arthritis (1). Interestingly, IFN is effective in controlling the arthritis-associated symptoms (8). This effect is possibly related to a decrease in the viral load. In contrast, the present case manifested arthritis after cessation of the IFN plus ribavirin treatment and based on serological and radiological findings, it is evident that RA occurred, rather than HCV-related arthropathy. Furthermore, RA occurred when HCV-RNA was no longer detectable. Therefore, an association between RA and the IFN plus ribavirin treatment was more likely than an association with HCV infection.

The increased prevalence of RF in patients with HCV infection diminishes the diagnostic specificity of RF for RA in patients. However, anti-cyclic citrullinated peptide (CCP) antibody is a highly specific biomarker for RA that has been shown to be useful for the diagnosis for RA in the HCV population (9). In the present case, sero-positivity for anti-CCP Ab also justified the diagnosis of RA. However, upon retrospective analysis, the present case had exhibited anti-CCP Ab before the start of the IFN plus ribavirin treatment. Recently, a remarkable gene-environment interaction has suggested a molecular mechanism for disease development in a subset of RA (10). The interaction between smoking and HLA-DRB1 SE genes was established as a risk factor for RA (11). In the present case, the possible interaction between SE and smoking may contribute to the seroconversion of anti-CCP Ab. However, our case did not exhibit any symptoms or signs of RA in the presence of high titers of anti-CCP antibodies. Antibodies to citrullinated pep-

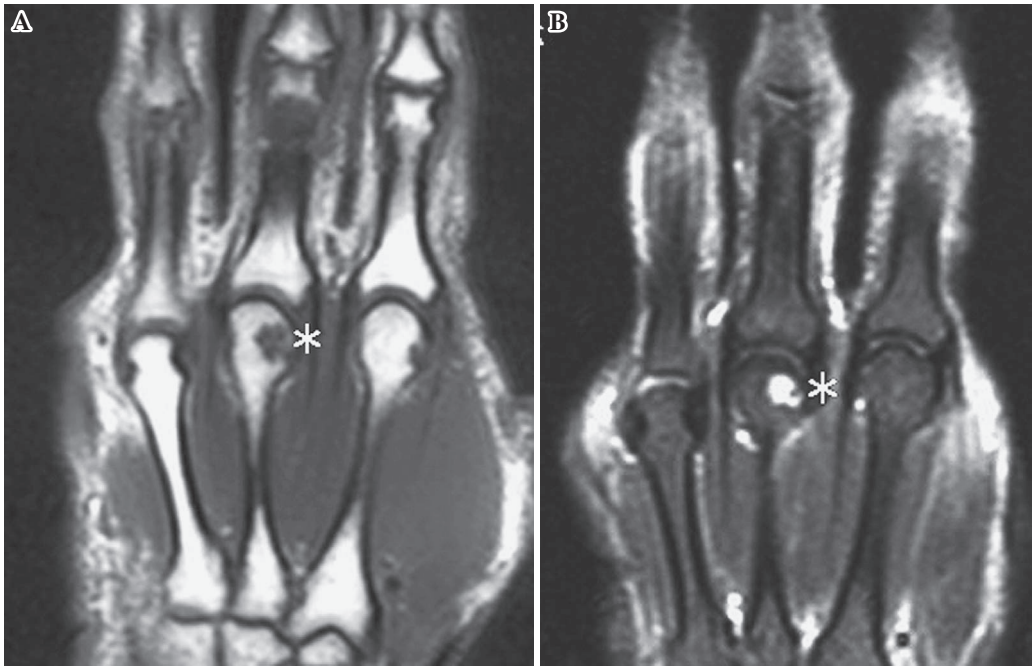
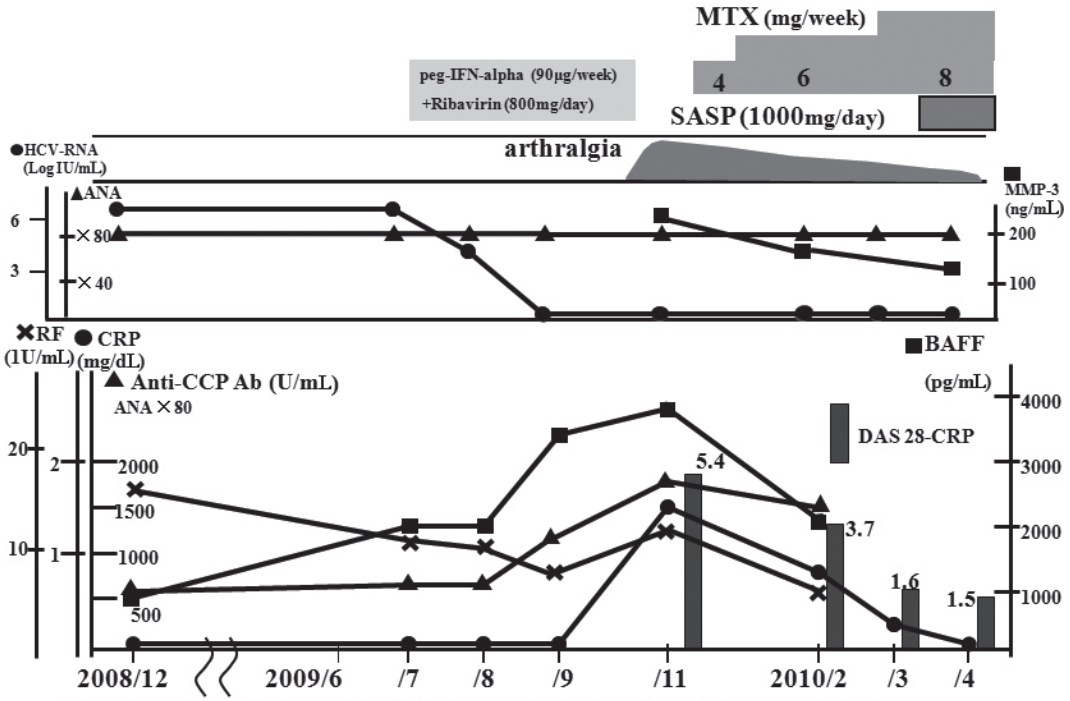


Figure 1. **T1-weighted (A) and STIR (B) magnetic resonance images (MRI) reveal bone erosion (asterisk), in third metacarpal bone.**



Abbreviations: ANA; anti-nuclear antibody, Anti-CCP Ab; anti-cyclic citrullinated peptide antibody, BAFF; B-cell activating factor of the tumor necrosis factor family, DAS 28-CRP; disease activity score 28 C-reactive protein, HCV; hepatitic C virus, IFN; interferon, MMP-3; matrix metalloproteinase 3, MTX; methotrexate, RF; rheumatoid factor, SASP; salazosulfapyridine

Figure 2. **Clinical course of the present patient. The titers of anti-cyclic citrullinated peptide antibodies and serum levels of BAFF were elevated after the induction of peg-IFN-alpha plus ribavirin treatment against HCV infection.**

tides have been demonstrated to precede the development of RA by several years (12), as observed in the present case. It is suggested that in addition to the synthesis of anti-CCP antibodies, additional events are needed to trigger the clinical onset of RA. In the present case, IFN-α treatment, an environmental factor in the context of smoking and the presence of the HLA-DR SE gene might have contributed to the onset of RA. Also, the association of high titers of anti-CCP

Ab and radiographic progression has been demonstrated (13). Alternatively, it is possible that sustained high titers of anti-CCP antibodies may have in part contributed to the RA onset and bone erosion seen in the present case.

IFN has multiple effects on the immune system, and can induce the development of autoimmune disorders (3). IFN therapy alters the cytokine profile inhibiting the production of IL-10 but maintaining that of IL-12 and TNF-α (14). Meanwhile ribavirin suppresses IL-10, IL-12 and TNF-α production (15). IFN was shown to induce macrophages to produce BAFF (16). More recently, it was demonstrated that IFN-α induced acceleration of lupus with increased circulating BAFF in NZB/W mice (17). In a human study, IFN treatment was demonstrated to trigger increased BAFF levels in patients with multiple sclerosis (18). In accordance with these findings, IFN-α plus ribavirin treatment markedly increased the serum levels of BAFF in the present case. BAFF, a B cell maturation and differentiation factor, plays a role in autoimmune reactions and autoantibody production (19) and elevated BAFF is related to autoantibody levels and synovitis in a subset of early RA patients and very early RA (20, 21). In the evaluation of serum BAFF levels during the preclinical RA stage, IFN plus ribavirin therapy strongly elevated BAFF in this case. Therefore, it is possible that the systemic induction of BAFF by IFN plus ribavirin therapy may facilitate the development of RA from SE/CCP-positive individuals. Considering the clinical course of the present case, we suggest a 2-step model for the pathogenesis of a subset of RA, in which the generation of anti-CCP antibodies precedes the disease, and in which a second environmental event may trigger the onset of RA.

In conclusion, we report a case of RA that occurred after the cessation of IFN-α plus ribavirin treatment against HCV infection. The present case suggests that biological agents, which may alter the cytokine network, can act as triggering factors for the development of RA in a population with genetic or environmental risk factors. Close surveillance for the occurrence of autoimmune diseases is needed in such individuals.

The authors state that they have no Conflict of Interest (COI).

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