Systemic Sclerosis after Interferon Alphacon-1 Therapy for Hepatitis C

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Abstract

A 66-year-old woman developed systemic sclerosis (SSc) after receiving interferon alphacon-1 (IFNαcon-1; consensus interferon) therapy for chronic hepatitis C. She suffered from Raynaud’s phenomenon about 1 year after a course of IFNαcon-1 therapy. The combination of proximal scleroderma, Raynaud’s phenomenon, and ANA positivity led to a diagnosis of systemic sclerosis (SSc). IFN has multiple effects on the immune system and is known to trigger the development of autoantibodies, as well as the onset or exacerbation of autoimmune disease. We suspect that the immunomodulatory effects of IFNαcon-1 triggered the clinical manifestations of SSc in this patient. To our knowledge this is only the third case of SSc after IFNα therapy, and it is the first case associated with IFNαcon-1 therapy.

Key words: systemic sclerosis, interferon alphi-con-1 therapy, consensus interferon, chronic hepatitis C

Introduction

Interferon alphi-con-1 (consensus interferon) is used as a treatment for chronic hepatitis C. IFNαcon-1 is novel synthetic recombinant interferon that was developed by comparing the amino acid sequences of several natural IFNα subtypes and assigning the most frequently observed amino acid to each position to generate a consensus molecule. When used to treat high-titer genotype 1 HCV infection, IFNαcon-1 has been shown to induce normalization of liver function in 44% of patients and a sustained viral response (SVR) in 26% (1). However, IFNα (including IFNαcon-1) has multiple effects on the immune system and it may trigger the development of autoantibodies or even the onset or exacerbation of autoimmune diseases such as autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, and polymyositis (2-5). Nevertheless, clinically overt autoimmune disease is rarely associated with IFNα therapy.

Case Report

A 66-year-old woman had been diagnosed as having hepatitis C virus infection in 1990. She had also suffered from pulmonary tuberculosis in 1960, and had been an anti-hypertensive therapy for 10 years. No relevant family history was noted. She did not have a past history or predisposing factors for autoimmune diseases. She was treated with IFNαcon-1 for genotype 1 chronic hepatitis C from September 2002 to February 2003 at our hospital. Daily administration of 18 MIU of IFNαcon-1 was done for 2 weeks, followed by 18 MIU three times weekly for 18 weeks. Before treatment, liver biopsy gave a diagnosis of chronic hepatitis (A2 and F2, activity grade 2/4, and fibrosis grade 2/4) (Fig. 1) and HCV viral load of 15 KIU/ml. After IFN therapy, she obtained a sustained viral response (SVR). And then she had no episode of any viral infection and no event that influences a network of cytokines. From February 2004, however, her fingers sometimes showed acrocyanosis.

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on cold mornings. In March 2004, she visited a dermatologist.

On examination, she was 156 cm tall and weighed 47.0 kg. Her temperature was 36.6°C and her blood pressure was 142/80 mmHg. The radial pulse rate was 87/min and regular. She had no signs of anemia or jaundice. Her fingers were sclerotic and edematous. There was no calcification of the skin or capillary vessel abnormality in the nail folds. There was no lymphadenopathy. Neurological examination revealed no abnormal findings.

Laboratory tests showed a red blood cell count of $4.33 \times 10^6/\mu$l, a white blood cell count of 4,900/μl, and a platelet count of $195 \times 10^3/\mu$l. The hemoglobin concentration was 12.8 g/dl. The levels of hepatobiliary enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), leucine aminopeptidase (LAP), γ-glutamyltranspeptidase (γ-GTP), and lactate dehydrogenase (LDH), were all normal. The C-reactive protein level was <0.2 mg/dl. Renal function tests showed that the blood urea nitrogen and creatinine levels were normal. Serology for hepatitis B virus was negative, while it was positive for hepatitis C virus.

The 50% hemolytic unit of complement (CH₅₀) level was 39 U/ml, and cryoglobulins were negative. Antinuclear antibody (ANA) was positive (1 : 640) with a diffuse pattern. No specific autoantibodies were detected, including rheumatoid factor, anti-SS-A, anti-SS-B, anti-ribonucleoprotein (RNP), anti-Sm, anti-centromere, anti-Scl-70 and antimitochondrial antibody (AMA).

Skin biopsy was performed at the extensor side forearm, and it showed atrophy of the epidermis with the dermis thickened (Fig. 2). In the deep layer of the dermis, collagen fibers were increased, while blood vessels and skin appendages were decreased. Overall, the histopathological features of the skin were compatible with SSc. The plain chest X-ray film and chest computed tomography showed chronic pleu-

Based on these clinical, radiological, and histopathological findings, as well as proximal scleroderma, Raynaud’s phenomenon, and ANA positivity, the diagnosis of SSc was established according to criteria defined by a Research Group of the Japanese Ministry of Health, Labour and Welfare in 1992 (6). The criteria of the American Rheumatism Association were also satisfied (7).

Treatment with tocopherol nicotinate gave symptomatic relief (Fig. 3). Six months later, routine laboratory tests (including liver function tests) were normal. ANA was still positive at 1 : 1280 with a diffuse pattern. In February 2005, however, Raynaud’s phenomenon became problematic again and cutaneous lesions were again noted. Nail fold bleeding was sometimes found.

**Discussion**

IFN has multiple effects on the immune system. It is well known that IFN may trigger the appearance of autoantibodies, as well as the onset or exacerbation of various autoimmune phenomena. Although the incidence of overt autoimmune disease associated with IFN treatment is only about 1-4%, autoantibodies can be detected in 20-60% of the patients receiving IFN therapy (8-10). Autoimmune thyroid disease is the most frequent manifestation, but nearly all autoimmune diseases (including rheumatoid arthritis, SLE polymyositis) can occur (2-5). In the present patient, ANA became positive at 1 year after IFN therapy. Six months later, the ANA titer increased further to 1 : 1280. We suspected that the immunomodulatory effects of IFNcon-1 had triggered the clinical manifestations of SSc in this patient. Two cases of SSc induced by IFNNo therapy have been reported before (11, 12). It has also been reported that bleomycin, docetaxel, and other chemotherapy drugs can induce
SSc (13, 14).

SSc is a multistystem disorder of unknown aetiology that is characterized by the deposition of excessive amounts of collagen in the skin and internal organs (15). Hallmarks of the disease are “leathery” skin and fibrosis of the affected organs. Activation of certain T lymphocyte subpopulations and fibroblasts plays a key role in the development of SSc (16). Studies of cytokines in SSc patients have shown a spontaneous increase of ‘fibrogenic’ cytokines, such as tumor necrosis factor-alpha (TNFα) and IL-1β, as well as impairment of mitogen-induced IFNγ production (17, 18). In particular, IFNγ is of great relevance because it is the most potent stimulator of HLA class II antigen expression by endothelial cells, thus promoting endothelial cell-leukocyte adhesion (18), but it is also a negative regulator of collagen production by fibroblasts (19). Both IFNα and IFNγ have been shown to inhibit collagen synthesis or dermal and synovial fibroblast proliferation stimulated by transforming growth factor beta (TGFβ) in vitro (20, 21), so these IFNs have been used to treat patients with SSc (22-25). However, IFNα might also paradoxically induce SSc as in our case. The mechanism is unclear but it could be related to the multiple potential effects of IFNα on the cytokine balance.

Whether or not the onset of SSc in the present patient after IFN therapy was directly due to IFN is controversial. Why did it take about 1.5 years from the initiation of IFN therapy for the symptoms of SSc to appear? We cannot exclude the possibility that SSc occurred incidentally, but she had no symptoms of collagen disease and ANA was negative before IFN therapy. HCV-RNA became undetectable soon after IFN therapy. Her early symptoms were relatively mild and only occurred on cold days, so symptoms might have been hard to recognize in the warmer seasons. Most cases of IFNα-induced autoimmunity occur during treatment and the disease improves with discontinuation of therapy. However, drug-induced autoimmune disorders are not always reversible and autoimmunity sometimes develops several months after IFN therapy (9, 26). Overall, we suspect that the immunomodulatory effects of IFNα on the cytokine balance.

In conclusion, we reported only the third case of SSc developing after IFNα therapy and the first case caused by IFNαcon-1. To avoid the occurrence or exacerbation of autoimmune disease, careful attention should be paid to signs and symptoms of autoimmunity in patients receiving IFN therapy both during and after treatment. Further studies are needed to elucidate the mechanism underlying the association between autoimmune disease and IFN therapy.

References


