Giant Negative T Waves during Interferon Therapy in a Patient with Chronic Hepatitis C

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Abstract

Interferon- α (IFN- α) has been widely used for treatment of chronic hepatitis C in Japan. In general, cardiovascular adverse reactions are rare in association with IFN- α therapy. Here, a 64-year-old man with chronic active hepatitis C complained of fatigue, palpitation and depression, and developed atrial fibrillation with prominent negative T waves during IFN- α therapy. Echocardiogram showed septal and apical hypertrophy. Three days after discontinuation of IFN- α , subjective symptoms and atrial fibrillation subsided. It is unclear whether or not IFN- α induced the giant negative T waves with apical hypertrophy. We might observe the developing course of hepatitis C virus (HCV) - related myocardial hypertrophy by chance. Cardiovascular toxicity should be carefully monitored during IFN- α therapy even in patients with minor cardiac disease, such as premature ventricular contracture (PVC) and mild hypertension.

(Internal Medicine 40: 105–109, 2001)

Key words: Interferon- α , giant negative T waves, hypertension

Introduction

Interferon (IFN) is the widely used for the treatment of hematological malignancies and chronic hepatitis. Virtually, all patients experience some toxicity during the therapy. Primarily, this involves flu-like symptoms such as fever, chills and malaise (1). However, transient leukopenia, asymptomatic increase in hepatic transaminase levels, somnolence, confusion and rash may occur. Cardiovascular toxicity related to IFN therapy, including hypotension and tachycardia, has been noted infrequently ranging from less than 5 to 12 percent (2). Gener-

ally, IFN-associated cardiovascular toxicity is considered to be very rare in the treatment of chronic viral hepatitis (3). We describe a patient with chronic active hepatitis C who was treated with IFN- α 2 and subsequently experienced supraventricular premature beats and atrial fibrillation with giant negative T waves.

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Case Report

A 64-year-old man was admitted to our hospital for treatment of chronic active hepatitis C on February 7, 1997. He had a past medical history of acute hepatitis in 1955, premature ventricular contracture (PVC), duodenal ulcer and mild hypertension since 1984. Thus, nicardipine and captopril have been administered for 12 years. On admission, his body temperature was 36.1°C, height 165 cm, weight 74 kg, and a body mass index 27.2 kg/m². On physical examination, the patient was alert and normotensive (120/68 mmHg) with a regular pulse rate (76/min), and heart murmur was not audible. The liver was palpable 3 cm beneath the right costal margin, dull edged and smoothly surfaced, vascular spider and palmar erythema were not observed. Neither systemic nor local edema was present. Laboratory findings were as follows: a hemoglobin concentration was 15.0 g/dl, a white blood cell count 6.0×10³/μl, and a platelet count 152×10³/μl. Serum levels of aspartate aminotransferase (81 IU/l; normal range, 11–32 IU/l), alanine aminotransferase (99 IU/l; normal range, 6–39 IU/l) and lactate dehydrogenase (490 IU/l; normal range, 236–455 IU/l) were modestly increased. Serum anti-hepatitis C virus (HCV) antibody (the 2nd generation, PHA method) was positive. Serum HCV-RNA was 0.56 MEQ/ml. HCV genotype (international classification) was 2b. On February 12, an electrocardiogram (ECG) tracing showed a regular rhythm left ventricular hypertrophy with a mild ST-T change (Fig. 1A). A chest radiograph

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Received for publication February 16, 1999; Accepted for publication August 2, 2000

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Figure 1. (A) Electrocardiogram prior to IFN- α treatment on February 7, 1997. (B) Electrocardiogram showing marked left ventricular hypertrophy and marked ST-T depression with prominent T wave inversion in precordial leads on March 17, 1997. (C) Electrocardiogram demonstrating giant negative T waves and atrial fibrillation with a ventricular rate of 111 beats per minute on March 19, 1997. (D and E) Electrocardiogram demonstrating giant negative T waves on March 31, 1997 and August 16, 1999.

Figure 2. UCG showing that the septal hypertrophy was slightly progressed during IFN treatment. IVST was 11 mm on February 12, 1997 (A) and 17 mm on March 19, 1997 (B). UCG showing apical hypertrophy (apical two chamber view, C) and septal hypertrophy (long axis view, D) on January 19, 2000.

revealed mild cardiomegaly, and the cardiothoracic ratio was 52.0%. Ultrasonic cardiography (UCG) findings were compatible to hypertensive heart (mild left ventricle hypertrophy, interventricular septal wall thickness at the mid portion, IVST: 12 mm, left ventricular posterior wall thickness, LVPWT: 12 mm) (Fig. 2A). At that time, apex was not carefully examined for hypertrophy. Abdominal echogram did not show a cirrhotic pattern. Based on the low HCV-RNA level, good prognosis genotype, and a chronic hepatitis pattern in the abdominal ultrasonography, diagnostic laparoscopy was performed to determine the clinical indication of IFN therapy. The liver specimen was histologically diagnosed as chronic active hepatitis. As shown in Fig. 3, IFN therapy was started on March 10, 1997; IFN- α 2b (Intron A, Schering-Plough, 10 million unit/day) was injected intramuscularly for nine days. In the first 4 days, he developed a high fever, but the fever subsided gradually thereafter. On March 17 (7th day of administration of IFN-

α), ECG during a regular check-up had already shown supraventricular premature beats with giant negative T waves (Fig. 1B). On March 19 (10th day of administration of IFN- α), the patient complained of fatigue, palpitation and depressive feeling. Serum levels of creatinine phosphokinase were within a normal limit. ECG showed tachycardia (100 beats per minutes) and supraventricular premature beats with giant negative T waves, and then atrial fibrillation emerged. UCG revealed septal and apical hypertrophy (IVST: 17 mm, LVPWT: 12 mm). The IFN therapy was discontinued. On the same day, the patient received digoxin 0.25 mg i.v., and from the next day, methyldigoxin 0.1 mg/day was administered. On March 21 (2 days after the cessation of the IFN therapy), ECG showed atrial fibrillation with giant negative T waves (Fig. 1C). On March 24 (4 days after the cessation of the IFN therapy), subjective symptoms improved and atrial fibrillation disappeared. On March 26 (7 days after cessation of the IFN therapy), UCG

Figure 3. Clinical course of this patient.

also showed septal and apical hypertrophy (IVST: 16 mm, LVPWT: 12 mm). On March 31 (11 days after the cessation of the IFN therapy), ECG still revealed giant negative T waves (Fig. 1D) and double Master test was negative. On August 16, 1999, ECG still revealed giant negative T waves (Fig. 1E). On January 19, 2000, UCG clearly revealed apical hypertrophy (apical two chamber view, C).

Discussion

There have been several reports documenting atrial fibrillation during or after IFN therapy. Most of them were from patients with malignancies, who were heavily treated with anticancer agents or had ischemic heart disease (4). Despite the conventional use of IFN-α, only 7 out of 11,241 (0.06%) patients with chronic hepatitis have reportedly developed cardiovascular complications (3, 5). Although cardiovascular complications are considered to be very rare in patients with chronic hepatitis as compared with those with malignant diseases receiving intensive chemotherapy, Teragawa et al have reported 6 patients with cardiovascular adverse effects during interferon therapy and 4 more patients within 1 year after the end of therapy (10/312, 3.2%), including arrhythmia (n = 4), ischemic heart disease (n = 4) and myocardial disease (n = 2) (6). Furthermore, Torsades de Pointes (7), non-sustained ventricular tachycardia (8), cardiogenic shock (9) and sinus bradycardia (10) were reported during IFN-α therapy for chronic hepatitis C. Accordingly, IFN-associated cardiovascular toxicity in the treatment of chronic hepatitis C might be more common than previously expected.

Interestingly, two reported cases (7, 8) and the present case had the same past history of PVC and mild hypertension controlled by anti-hypertensive drugs. High age, taking anti-hypertensive drugs and transient PVC may induce cardiac complications when IFN therapy is added. Careful cardiac monitoring should be required in these patients.

Matsumori et al have intensively reported that HCV infec-

tion may contribute to the development of cardiomyopathy (11–13). Recently, Matsumori et al have reported that 6 out of 9 HCV patients with hypertrophic cardiomyopathy showed ace-of-spades-shaped deformities of the left ventricle with apical hypertrophy (14). However, these reports from Japan are in disagreement with those from Greece, Germany and Italy (15–17). Dalekos et al have not indicated a pathogenic link between HCV infection and cardiomyopathy (15). They have speculated that genetic or other factors could be the reason for this discrepancy. The relationship between HCV infection and cardiomyopathy is still controversial. Furthermore, no reports have discussed a history of IFN therapy.

It is important to contemplate what factor induced the giant negative T waves during only four weeks in this case. First, we observed that myocardial hypertrophy induced by HCV had just begun incidentally. Second, IFN with or without anti-hypertensive drugs (captopril and nicardipine) induced myocardial hypertrophy. When the giant negative T waves emerged, symptoms of infection were not observed. At this time, we did not use additional treatment except for IFN, and had to discontinue it because of adverse reactions. Although IFN-induced myocardial hypertrophy in experimental models have not been reported, Omae et al have reported septal/left ventricle posterior wall hypertrophy 9 days after the start of treatment of IFN, but they did not discuss the previous status (8).

In summary, we reported a rare case in which giant negative T waves and atrial fibrillation developed during IFN therapy for chronic hepatitis C. Coincidental HCV-induced or IFN-induced apical hypertrophy was speculated. Careful cardiac monitoring is required in patients with trivial cardiac medical history, such as PVC or hypertension during the IFN therapy.

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