Multiple Myeloma Complicated by Congestive Heart Failure Following First Administration of Recombinant α-Interferon

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A 59-year-old female was admitted to Tsukuba University Hospital and diagnosed as IgA-λ multiple myeloma (stage IIIA). No cardiovascular disorder with the exception of minor ischemic changes in ECG was revealed before treatment. Recombinant human α-interferon (IFN) at a dose of 3 million units combined with melphalan and prednisolone was administrated. Sixteen hours after the first administration of IFN, IFN was suspended by the symptoms of congestive heart failure (CHF). Treatment with diuretics and catecholamine products showed almost complete recovery from CHF in 3 weeks. An adverse reaction to IFN was strongly suspected as the cause of CHF.

Key words: adverse reactions, abnormal electro-cardiogram

Introduction

Interferon (IFN), primarily found as an anti-viral agent, has also been demonstrated to have anti-tumor activity in vitro and in vivo (1–4). Therapeutical effects of IFN on renal cell carcinoma, multiple myeloma, hairy-cell leukemia, chronic myelogenous leukemia, and non-Hodgkin’s lymphoma have been documented (5–9). Adverse reactions to IFN include fever, which frequently appears, nausea, vomiting, fatigue, leukocytopenia, and thrombocytopenia (10–15). Reactions involving the circulatory system are not rare (13–16) although the incidence of congestive heart failure (CHF) during IFN therapy is very low. We report here a patient with multiple myeloma in whom CHF occurred following the first administration of recombinant human α-IFN. Adverse reaction of the myocardium and/or cardiovascular system to α-IFN inducing CHF is reviewed and the relation of the present case to those in the literature is discussed.

Case Report

A 59-year-old female was admitted to Tsukuba University Hospital in February 1989, for the treatment of multiple myeloma. The diagnosis of multiple myeloma had been made in October 1988, and she had been treated with a combination chemotherapy of melphalan, prednisolone (PSL), and methotrexate, at another clinic. She had no past history of cardio-pulmonary disorders. On admission to our hospital, heart rate was 76/min without irregularity and blood pressure was 160/78 mmHg. She was slightly anemic, however, no heart murmur ausculated. Neither hepatosplenomegaly nor any symptoms of CHF were found. Hematological examinations revealed a hemoglobin level of 8.7 g/dl, leukocyte 1,000/μl, and platelet 37,000/μl. Bone marrow aspiration from the sternum revealed myeloma cells with distinct nucleoli in 81.2% of the nucleated cells. Erythrocyte sedimentation rate was 152 mm/h, and total protein 9.3 g/dl, serum albumin 3.1 g/dl, serum IgA 4,710 mg/dl (remarkably increased), IgM 76 mg/dl (at the lower limit of normal), and IgG 353 mg/dl (less than the normal value). Blood urea nitrogen was 7.0 mg/dl, the serum creatinine 0.9 mg/dl, and creatinine clearance 36.6 ml/min. Blood chemistry for liver function within normal limits. Examination of urine revealed protein of 3.5 g/day, N-acetylg glucosaminidase (NAG) 45.2 IU/l, and β2-microglobulin 34.0 mg/day. These findings suggested the functions of both glomeruli and tubules were impaired. Immunoelectrophoresis revealed IgA-λ type M protein in the serum and Bence-Jones (λ) protein in the urine. Increased plasma viscosity was shown by the measurement using a rotational viscometer. Minor
α-Interferon and Heart Failure

Fig. 1. ECG. A) ECG on admission. Inverted T waves in V2, V3, flat T waves in V4, V5 and inverted U waves with ST-segment depression in V4–V6. B) ECG on February 17 (2 days after CHF) showing inverted T waves in V2, V3 with increased; the flat T wave in V4 became negative. ST-segment depression in V4–V6 were normalized (Fig. 1). Neither a fluid imbalance nor acute cardiovascular disorder was found. As we suspected an adverse reaction to IFN as a cause of CHF, the administration of IFN was suspended. Chemotherapy consisting of melphalan and PSL was continued thereafter. Treatment with diuretics, cardiac glycoside and catecholamine products resulted in a remarkable improvement of cardiopulmonary function (Fig. 2). Inverted T waves in V4 returned to flat but unaltered waves in V2, V3 (Fig. 1), however, she recovered from CHF almost completely in approximately

abnormalities in the electro-cardiogram (ECG) (inverted T waves in V2, V3, flat T waves in V4, V5 and inverted U waves with ST-segment depression in V4–V6) were found on admission (Fig. 1). Chest X-ray showed no abnormalities. Left ventricular hypertrophy was most likely, however, myocardial ischemia could not be excluded. Before chemotherapy, ultrasonic cardiography (UCG) was not performed.

Based on her good performance status (grade 1) and the fact that the abnormalities of the cardio- and renal-functions were minor, we considered her to be tolerant of α-IFN treatment combined with melphalan and prednisolone. At 8 PM on February 15, 1989, 5 hours after the first intramuscular injection of 3 million units of IFN, 10 hours after the oral administration of 2 mg melphalan and 10 mg PSL, and she vomited without any remarkable changes in vital signs. Thereafter, her body temperature gradually rose to 39°C by the following morning. She again vomited, 16 hours after the first administration of IFN, and her consciousness level declined. Blood gas analysis showed hypoxemia with a PaO2 of 42.8 mmHg. Based on chest X-ray findings showing pulmonary congestion, increased central venous pressure, and reduced fractional shortening and wall motion on UCG, a diagnosis of CHF was made. On ECG, inverted T waves in V2, V3 increased in magnitude and T wave in V4 became inverted. ST-segment depressions in V4–V6 became inverted. ST-segment depressions in V4–V6 were normalized (Fig. 1). Neither a fluid imbalance nor acute cardiovascular disorder was found. As we suspected an adverse reaction to IFN as a cause of CHF, the administration of IFN was suspended. Chemotherapy consisting of melphalan and PSL was continued thereafter. Treatment with diuretics, cardiac glycoside and catecholamine products resulted in a remarkable improvement of cardiopulmonary function (Fig. 2). Inverted T waves in V4 returned to flat but unaltered waves in V2, V3 (Fig. 1), however, she recovered from CHF almost completely in approximately

Fig. 2. Ultrasonic cardiography, short-axis parasternal echocardiography, at the level of papillary muscles during the diastolic phase (left) and systolic phase (right) on February 22 (A) (6 days after CHF). Fractional shortening was reduced (23%) and generalized hypokinesis of left ventricle was found. Echocardiography on April 3 (B) (47 days after CHF) showed normalized fractional shortening (33%) and improved wall motions.
During the recovery phase from CHF, her renal function was gradually lowered. Plasmaphereses were performed to alleviate hyperviscosity, and subsequently serum creatinine was lowered and creatinine clearance was slightly improved (Fig. 3). Although chemotherapy consisting of melphalan and PSL was continued, serum M component was not normalized and the serum calcium concentration was gradually elevated. In May, her consciousness level gradually declined again. Serum levels of IgA, calcium, and creatinine were not lowered, while several plasmaphereses and a hemodialysis were performed. At this time, the myeloma itself was refractory to chemotherapy and systemic candidiasis developed. She died of candidiasis and hemorrhagic complication on May 30, 1989 (Fig. 3). Autopsy revealed infiltration of myeloma cells not only to the bone marrow of thoracic and lumbar vertebrae, sternum, and ribs, but also to the liver, spleen, kidneys, adrenal glands, stomach, pancreas, and lungs. No deposition of amyloid was found in the kidneys, but so-called “myeloma kidneys” (deposition of protein-like substances in tubules) were demonstrated. Systemic lesions of candidiasis were also found. Autopsy revealed neither infarction, infiltration of myeloma cells, nor deposition of amyloid in the myocardium (Fig. 4).

**Discussion**

Adverse reactions frequently seen with IFN treatment include fever, nausea, vomiting, fatigue, leukocytopenia, and thrombocytopenia, most of which are reversible and tolerable (10–15). However, there have been a few reports of serious adverse reactions to IFN. Adverse reactions other than CHF related to the circulatory system which are observed during or immediately after the administration of IFN include hypotension, sudden death, and acute myocardial infarction (13). Supraventricular or ventricular arrhythmias, and dilated cardiomyopathy have also been reported (17). CHF reported in relation to the treatment with α-IFN are rare (16–22), γ-IFN very rare (23, 24), and no reports with β-IFN in
the literature (25). The previous reports of CHF as a complication of α-IFN treatment are summarized in Table 1. In 7 out of 10 cases of such CHF, considerable doses of α-IFN had been administered over a long period before the development of CHF. There are two cases reported by Sarna et al (15) and by Sachs et al (16), in which CHF occurred soon after the first administration of IFN. The short period from the administration of IFN to the onset of CHF in these cases including the present case may suggest an allergic reaction to IFN. The mechanism of the adverse reactions to IFN involving the circulatory system is not well documented. Concerning the effect of IFN on myocardial cells, Blalock and Stanton showed that mouse leukocyte-derived IFN has a stimulative effect on beat frequency in cultured mouse myocardial cells similar to that of norepinephrine (26). In contrast, Lampidis and Brouty-Boyé reported an opposite effect of IFN on the beat frequency in cultured rat myocardial cells (27). Other speculations concerning the effects of IFN on the heart include direct inhibition of neogenesis of muscle-contracting protein, inducing coronary spasm (20), and stimulation of autoimmune or inflammatory reactions by a complex of IFN and cardiac tissue (22), however, neither has been confirmed yet. Patients with multiple myeloma, including the present case, often have several risk factors which may develop CHF, such as anemia, renal dysfunction, or hyperviscosity. The clinical course of the present case, often have several risk factors which may develop CHF, such as anemia, renal dysfunction, or hyperviscosity. The clinical course of the present case may suggest an allergic reaction to IFN. The short period from the administration of IFN with the development of CHF. Such an immediate type of adverse reaction to IFN may be rare, however this should be taken into account on the first administration of IFN, especially to patients with multiple myeloma, as they often have dysfunctions of the circulatory system.

References


Table 1. α-Interferon-Related Heart Failure

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Disease</th>
<th>Dose</th>
<th>Duration of therapy</th>
<th>Outcome</th>
<th>Reference No.</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/M</td>
<td>Lung cancer</td>
<td>3 MU*</td>
<td>4 hours</td>
<td>dead</td>
<td>15</td>
<td>1983</td>
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<tr>
<td>2</td>
<td>ND</td>
<td>Hepatocellular carcinoma</td>
<td>ND</td>
<td>1st administration</td>
<td>ND</td>
<td>16</td>
<td>1985</td>
</tr>
<tr>
<td>3</td>
<td>ND</td>
<td>Breast cancer</td>
<td>750 MU/m²</td>
<td>9 weeks</td>
<td>alive</td>
<td>18</td>
<td>1985</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>Multiple myeloma</td>
<td>10 MU/m²</td>
<td>ND</td>
<td>alive</td>
<td>19</td>
<td>1986</td>
</tr>
<tr>
<td>5</td>
<td>73/F</td>
<td>Non-Hodgkin's lymphoma</td>
<td>362 MU/m²</td>
<td>32 weeks</td>
<td>alive</td>
<td>20</td>
<td>1988</td>
</tr>
<tr>
<td>6</td>
<td>62/F</td>
<td>Renal cell carcinoma</td>
<td>27 MU</td>
<td>5 days</td>
<td>alive</td>
<td>17</td>
<td>1988</td>
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<tr>
<td>7</td>
<td>35/M</td>
<td>Kaposi's sarcoma</td>
<td>2,695 MU</td>
<td>11 weeks</td>
<td>alive</td>
<td>21</td>
<td>1989</td>
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<tr>
<td>8</td>
<td>37/M</td>
<td>Kaposi's sarcoma</td>
<td>7,938 MU</td>
<td>103 weeks</td>
<td>alive</td>
<td>21</td>
<td>1989</td>
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<tr>
<td>9</td>
<td>42/M</td>
<td>Kaposi's sarcoma</td>
<td>1,700 MU</td>
<td>57 weeks</td>
<td>alive</td>
<td>21</td>
<td>1989</td>
</tr>
<tr>
<td>10</td>
<td>74/M</td>
<td>Hairy cell leukemia</td>
<td>540 MU</td>
<td>26 weeks</td>
<td>alive</td>
<td>22</td>
<td>1990</td>
</tr>
<tr>
<td>11</td>
<td>59/F</td>
<td>Multiple myeloma</td>
<td>3 MU</td>
<td>16 hours</td>
<td>alive</td>
<td>present case</td>
<td>1992</td>
</tr>
</tbody>
</table>

* Leukocyte interferon; MU: million units; ND: not described.