Recurrence of Sarcoidosis Following Interferon Alpha Therapy for Chronic Hepatitis C

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We report a 67-year-old male patient with a known history of sarcoidosis in remission who had recurrent sarcoidosis following a five-month administration of interferon alpha (IFN-α) for chronic hepatitis C. He developed bilateral swelling of the parotid glands and bilateral diffuse reticulonodular pulmonary parenchymal opacities on chest roentgenograms. Serum angiotensin converting enzyme (ACE) levels and soluble IL-2 receptor levels were high and a transbronchial lung biopsy revealed noncaseating granulomas. The abnormalities on both laboratory data and chest roentgenograms were resolved after administration of oral prednisolone.

Key words: granuloma, IFN-α, soluble IL-2

Introduction

IFN may induce antiviral, antigrowth and immunomodulatory effects (1). IFN-α is known to suppress viral replication and to restore elevated serum aminotransferase levels, leading to an improvement in the histological changes in the liver in patients with chronic hepatitis C (2, 3). However, IFN-α is also known to induce various autoimmune disorders, such as interstitial pneumonia, systemic lupus erythematosus, autoimmune hemolytic anemia, hypothyroidism and immune thrombocytopenia (4–9). Here, we describe a patient with symptoms, and radiographic and pathologic changes indicative of recurrent pulmonary sarcoidosis following IFN-α therapy for chronic active hepatitis C.

Case Report

A 67-year-old nonsmoking male with shortness of breath and chronic hepatitis was diagnosed as having sarcoidosis in December 1978, because partially resected right parotid gland and transbronchial lung biopsy specimens showed noncaseating granulomas, and there was a high serum ACE level. Further, bilateral hilar lymphadenopathy with bilateral parenchymal reticulonodular opacities on chest roentgenograms were present. He was treated at that time with oral prednisolone for swelling of bilateral parotid glands and shortness of breath. Over the subsequent month, the abnormal findings on chest roentgenograms and the high serum ACE level were gradually resolved, the swelling of the parotid glands and shortness of breath disappeared, and oral prednisolone therapy was tapered off. However, slight liver damage continued. In June 1993, 15 years after the diagnosis of sarcoidosis, the presence of antibody to the hepatitis C virus was detected. A transcutaneous liver biopsy disclosed destruction of the limited plate, portal mononuclear infiltration and piece-meal necrosis, which were compatible with the findings of chronic active hepatitis. IFN-α therapy was started on December 1, 1993 for chronic active hepatitis C. Five months after the IFN-α therapy was begun, the patient complained of swelling of both parotid glands and shortness of breath, and the chest roentgenograms revealed diffuse reticulonodular pulmonary parenchymal opacities (Fig. 1). In May 1994, when he had taken a total amount of 60 million units of IFN-α, high-resolution computed tomographic scans of lungs confirmed diffuse small nodular lesions (Fig. 2). He had not newly taken any medicine. A 67Ga citrate scan showed increased radiogallium uptake in both lung parenchyma, the mediastinum or both hilar lymph nodes and both parotid glands (Fig. 3). Transbronchial lung biopsy specimens revealed noncaseating granulomas with lymphocyte infiltration consistent with sarcoidosis (Fig. 4). A bronchoalveolar lavage was also performed, and all stains and cultures were negative for fungal, acid-fast bacilli and other bacterial infections.

Laboratory studies on admission revealed a hematocrit of 41% and a white blood cell count of 4,300/μl, with normal
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differentials. Blood chemical analysis demonstrated normal aspartate aminotransferase, alkaline phosphatase, albumin, and total protein, but lactic dehydrogenase was slightly elevated at 147 IU/l (normal, 49–92 IU/l). Serum calcium was normal and serum angiotensin converting enzyme (ACE) was high, 30.2 IU/l (normal, 8.2–21.4 IU/l). Analysis of bronchoalveolar lavage fluid revealed that the total cells were $1.46 \times 10^7$/ml; macrophages, lymphocytes and neutrophils of the recovered cells were 10.2% and 88.8% and 1.0% respectively. Cell surface marker studies of the bronchoalveolar lavage showed the following results; CD4+ 72.3%, CD8+ 21.3%, CD3+ 97%, CD4:CD8 3.3 and HLA-DR+ CD4+ 59.9%, HLA-DR+ CD8+ 16.6%, HLA-DR+ CD3+ 68.4%. The serum soluble IL-2 receptor was high at 1,800 U/ml (normal, 120–384 U/ml). An arterial
blood specimen while breathing room air revealed pH 7.43, PaO₂ 58.6 mmHg, and PaCO₂ 39.2 mmHg. Pulmonary function tests showed a vital capacity of 3.42 (107% of predicted), a forced expiratory volume of 2.21 (67% of predicted), and a lung diffusion capacity of 15.25 (84% of predicted). Under a presumptive diagnosis of IFN-α induced recurrent sarcoidosis, IFN-α therapy was discontinued and oral prednisolone therapy was begun at a dose of 30 mg daily with prompt resolution of the radiographic abnormalities and symptoms.

Discussion

Sarcoidosis, a multisystem granulomatous disorder of unknown etiology, presents most frequently with bilateral hilar lymphadenopathy, and pulmonary parenchymal lesions and sometimes with ocular and skin lesions. The diagnosis of sarcoidosis requires appropriate chest roentgenogram findings, clinical symptoms, histologic demonstration of noncaseating granulomas, and exclusion of other infections and neoplastic causes. We diagnosed the present case as recurrent sarcoidosis, based on the following findings: 1) the presence of bilateral hilar lymphadenopathy and parenchymal reticulonodular opacities on chest roentgenograms; 2) the presence of bilateral swelling of the parotid glands; 3) a high serum ACE level; 4) the presence of noncaseating granulomas in the right parotid gland and lung parenchyma; 5) all of the above findings were observed in both episodes (1978 and 1993).

IFN was originally described as a protein capable of inducing antiviral activity in cells (1). Subsequently, it was found that many different interferon types exist and that they exert various effects on the immune system, including modulation of immunoglobulin production as well as stimulation of T cell cytotoxicity, macrophage functions, and natural killer cell activity. Consequently, the use of interferons in the treatment of chronic hepatitis C is increasing (2, 3).

Interstitial pneumonia may possibly be induced by IFN-α administration. The incidence of IFN-α-induced interstitial pneumonia is particularly high when IFN-α is used in combination with some type of herbal medicine (Sho-Saiko-To) (4). However, the present patient did not take any other drugs and no herbal medicines. Incidences of IFN-α-induced interstitial pneumonia after two months and after a total dose of over 100 x 10⁶ I.U. are noted to be higher. Although the pathogenesis of this disease remains unclear, presence of some cytokines from mononuclear cells which are activated by IFN-α might play a role in producing interstitial pneumonia.

Recently, there have been two abstracts and one case report documenting the developing of sarcoidosis following IFN (IFN-α, IFN-2b, IFN-γ) therapy (10-12). Abdi et al (10) observed sarcoid granuloma in transbronchial lung biopsies of patients with advanced renal cell carcinoma following IFN-α therapy and discussed malignancies associated with sarcoid-like granuloma. To our knowledge, none of the patients in any reports had clinical or radiographic abnormalities to suggest recurrent IFN-α induced pulmonary parenchymal sarcoidosis without malignancy.

Sarcoidosis is characterized in its early stage by T-helper lymphocyte alveolitis, and active T lymphocytes may be involved in the lesion with granuloma. Lung mononuclear cells in sarcoidosis are known to release IFN (13), and IFN is an important mediator of granulomatous lung disorders (13-16). Amaya and coworkers suggested that oligo-2',5'-adenylate synthetase (2, 5 AS) which may induce by all types of IFN (17) contributes to the pathogenesis of sarcoidosis. T lymphocytes activated by IFN-α are known to produce IFN-γ and IL-2 which may stimulate T lymphocyte and macrophage activity and IFN-α may induce sarcoidosis (1, 8). However the pathogenesis of sarcoidosis in our patient is not clear.

Most cases of sarcoidosis have spontaneous remission and a favorable outcome, but in a few cases it is chronic with variable disease activity over many years. Sarcoidosis is found worldwide, although it has predilections for certain areas and races. The worldwide resolution rate of asymptomatic patients presenting with bilateral hilar lymphadenopathy (Stage I) ranges from 53-87% (18, 19). Although the effectiveness of IFN therapy has been substantiated in some malignancies, chronic hepatitis C, and some infectious diseases (20), we emphasize attention to the possibility of recurrence of sarcoidosis in patients receiving IFN therapy who have had a history of sarcoidosis. Even if sarcoidosis is not present when IFN therapy is initiated, the patient’s past history should be checked carefully for the occurrence of sarcoidosis.

In summary, we reported a rare case in whom sarcoidosis recurred following IFN-α therapy for chronic hepatitis C. This case suggests the possibility that IFN-α may be involved with, or may trigger the sarcoid reaction.

References

11) Liozon E, Cransac M, Remenieras L, Cathy-Thomas I, Vovor A, Bordessoule D. La Sarcoidose: Une nouvelle complication de traitement
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