Interferon-induced Granulomatous Lung Disease

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INTRODUCTION

Interferons are used to treat various internal and dermatological diseases. Exogenously administered interferons stimulate the Th-1 response, which plays a major role in granuloma formation. Interferon therapy can induce or exacerbate sarcoidosis. In most of the patients with interferon-induced sarcoidosis, the disease subsides when interferon is discontinued. Occasionally, treatment with corticosteroids may become necessary. Four unusual cases of interferon-induced sarcoidosis and review of the recent relevant literature on this subject are presented.

CASE REPORTS

Case 1

In 1992, this 49-year-old Caucasian woman developed hepatitis. She was given interferon-alpha and ribavirin. After three months, the patient developed dry cough and dyspnea on moderate exertion. Physical examination revealed only bilateral, fine crackles occupying the lower parts of both lungs. A chest roentgenogram showed mild reticulo-nodular changes, but the chest CT scan was consistent with moderate interstitial lung disease. Gallium scan was markedly positive. Lung biopsy showed non-caseating granulomas. The patient also had an elevated serum angiotensin-converting enzyme level, hypercalcemia, and hypercalciuria. The diagnosis of multi-system sarcoidosis was clear. It was decided not to give her prednisone, but to discontinue the interferon-ribavirin combination. After a few months, her sarcoidosis subsided; chest CT scan, serum angiotensin converting enzyme, and serum calcium levels became normal.

In this patient multisystem sarcoidosis developed approximately three months after the start of interferon-ribavirin and underwent natural remission once the drug was stopped. The occurrence of hypercalciuria in the patients with interferon-induced sarcoidosis has not been reported before.

Case 2

A 53-year-old Caucasian woman was diagnosed with hepatitis C five years prior to this presentation. She was given interferon-alpha. Six months after the initiation of therapy, the patient developed moderate dyspnea. A month later she noticed skin nodules on the arms and legs. Her old tattoo became tender and indurated (Figure 1). A chest x-ray revealed interstitial-nodular infiltrate. The lung function tests, gallium scan, serum angiotensin-converting enzyme and calcium levels were normal. Skin biopsies of the nodule showed noncaseating granuloma (Figure 2).

In this patient, sarcoidosis ushered in with reactivation of the previous tattoo scar and subcutaneous nodules.

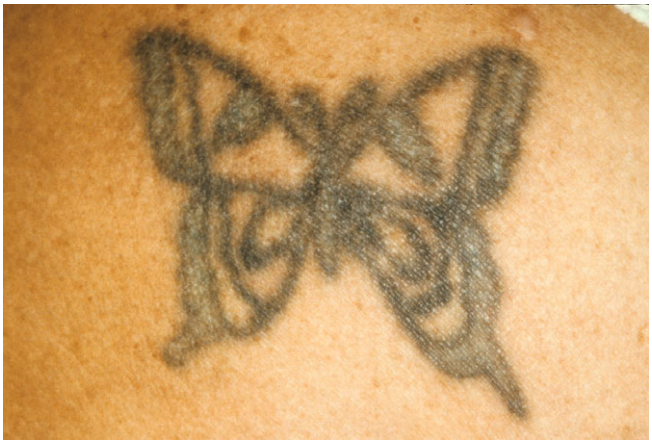

Figure 1. Tattoo became itchy and tender. A nodule appeared indicating the onset of sarcoidosis.

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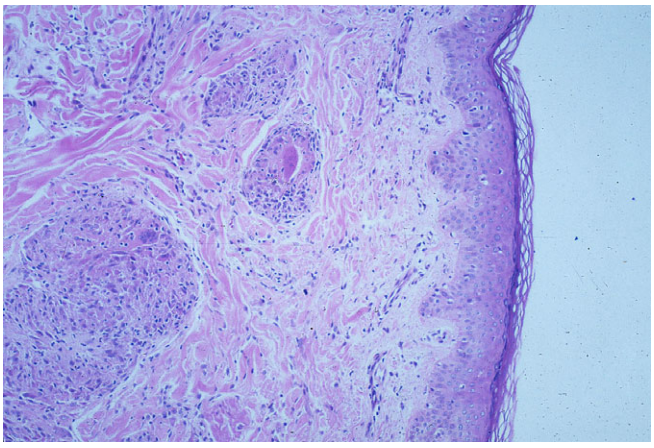

Figure 2. A biopsy of the lesion showed non-caseating granuloma consistent with sarcoidosis.

Case 3

In 1997, at the age of 63 years, this Hispanic man was given interferon-ribavirin for hepatitis C. He continued the treatment for two years. His liver functions became normal and the viral load came down. A few months later he developed hypothyroidism thought to be due to interferon treatment. In 2002, the patient started noticing fatigue and dyspnea. A chest x-ray showed interstitial infiltrates. A trans-bronchial lung biopsy showed non-caseating granuloma. The lung function study showed a vital capacity of 75% and diffusing capacity of 65% of predicated normal. He was treated with prednisone 20 mg day.

In this patient sarcoidosis developed after the two-year course of interferon was completed. The patient developed two clinical syndromes related to interferon; hypothyroidism and sarcoidosis. His sarcoidosis was mild and responded to treatment.

Case 4

This 55-year-old Caucasian man was given interferon-ribavirin for hepatitis C. After four months he developed renal insufficiency and hypothyroidism. The treatment was stopped. After a few months he became confused, forgetful, and lethargic. The diagnosis of neurosarcoidosis was considered. A chest x-ray showed hilar adenopathy. A lymph-node biopsy showed non-caseating granuloma. MRI of the brain revealed lepto-meningial enhancement consistent with neurosarcoidosis. Spinal fluid sample showed lymphocytosis. He was treated with prednisone. He improved in four weeks but developed corticosteroid-induced side effects. He was place on hydroxy-chloroquine. He made an excellent recovery.

DISCUSSION

Interferons are antiviral cytokines. They influence cell growth and modulate the immune system [1]. There are two classes of interferons:

Class Ⅰ interferons: Almost any cell type in response to viral and other infections can produce interferon-alpha and interferon-beta. They are encoded by at least 8 genes clustered on chromosome9, made up of 165 or 166 amino acids, and have a molecular weight of approximately 20 kD.

Class Ⅱ interferons: Interferon-gamma is produced by T-cells and natural killer cells, is encoded by a single gene located on chromosome 12, made up of approximately 127 to 143 amino acids, and has a molecular weight of approximately 90 kD. Interferon-gamma has effects similar to those of class Ⅰ interferon.

Interferon-alpha is effective in hepatitis-C, chronic idiopathic myeloid leukemia, myelofibrosis, cutaneous T-cell lymphoma, multiple myeloma, melanoma, follicular B-cell lymphoma and hairy cell leukemia. Interferon-alpha has been shown to benefit patients with pulmonary metastases. Interferon-beta is mainly used to treat multiple sclerosis. Interferon-gamma is used for chronic granulomatous disease and has also been tried to control idiopathic pulmonary fibrosis.

The common side effects of interferons are fever, chills, chest tightness, bone and muscle aches, headaches, and depression. Interferons may exacerbate autoimmune disorders including lupus erythematosus, hemolytic anemia thyroiditis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, monoclonal gammopathy, and nonspecific polyarthropathy. Some of these patients had evidence of a preexisting sub-clinical illness that was triggered by interferon. In other patients the drug appeared to have caused de novo appearance of the illness.

How does exogenously given interferon-alpha cause the granulomatous syndrome?

It has been suggested class Ⅰ and Ⅱ interferons share signal transduction pathways. Exogenously administered interferon-alpha and interferon-beta can activate macrophages in vitro. Interferon-alpha influences the production of interferon-gamma, reduces the activation of Th2 lymphocytes, increases the expression of mRNA coding for IL-12, and together with IL-12 leads to Th1 differentiation and increased production of the corresponding cytokines. Ribavirin, a nucleoside analogue of guanosine is an active medicine, in vivo and in vitro, against RNA and DNA viruses. Because of its virostatic activity it is used in treating many viral infections. Ribavirin enhances the Th-1 response by increasing the production and expression of IL-12 mRNA, by increasing production of interferon- and tumor necrosis factor, and decreasing the Th-2 response.

The superiority of the interferon-alpha-Ribavirin combination in enhancing the Th1-type immune response may be responsible for an exaggerated granulomatous response [10]. Mice immunized with HCV core protein in the presence of ribavirin showed increased production of IL-12 that promotes the differentiation of CD4 cells to Th1 cells.

Does systemic sarcoidosis differ from the type of sarcoidosis induced by interferon-alpha or the combination of interferon-alpha and ribavirin?

To our knowledge there are only 34 cases of interferon-induced sarcoidosis in the English literature, including the four described herein [2]. Only 2 of 34 (6.7%) had a previous history of sarcoidosis. Thus in 32 patients sarcoidosis appeared after interferon therapy. Twenty-six of thirty-four (75.8%) had evidence of multisystem sarcoidosis]; seven patients only cutaneous sarcoidosis and one had only neurosarcoidosis. In 26 of 34 cases (75.8%), interferon-alpha was used to treat hepatitis C; four cases received the drug for myelogenous leukemia (CML), and the remaining four had multiple myeloma, multiple sclerosis, and thrombocythemia [32]. This group of 34 patients included 19 women and 15 men, ranging from 26 to 67 years in age with a mean of (48.61 ± 9.45 years). Fourteen patients received interferon-alpha alone; 13 patients received interferon-alpha and ribavirin; two patients received interferon-alpha, ribavirin, and amantadine 11]; and three patients were given interferon-gamma. Sarcoidosis developed during interferon treatment in 27 patients and after the termination of treatment in seven. In one of our patients, sarcoidosis appeared approximately 12 to 14 months after the discontinuation of treatment. In the patients receiving interferon therapy, the appearance of symptoms suggesting a new multi-system disease should lead a physician to think of sarcoidosis as one of the diagnoses. Chest x-ray and serum ACE levels should be obtained. In most of the patients sarcoidosis disappears when interferon discontinued. We have followed one such patient; her sarcoidosis has not recurred during the six-year follow-up. Furthermore, these patients respond favorably to corticosteroids with or without stopping interferon.

REFERENCES

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