Could a Six-Month Course of Pegylated Interferon-α2a and Ribavirin for Hepatitis Virus C Trigger Sarcoidosis? A Case Report and Literature Review

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Abstract

Sarcoidosis is a chronic inflammatory multisystem disease of unknown etiology. We report on a 57-year-old woman presenting with typical sarcoidosis occurring two months after completion of a six-month course of interferon-α (IFN-α) and ribavirin for chronic hepatitis C virus (CHC) infection. The current observation is interesting with regard to the time elapsed between symptoms occurrence and antiviral treatment withdrawal and spontaneous recovery after ten months of follow-up. Pathophysiological mechanisms involved in the development of antiviral therapy-induced sarcoidosis are discussed in the present article.

Keywords: Chronic hepatitis C; Interferon-alpha and ribavirin combination therapy; Sarcoidosis; Spontaneous recovery
Sarcoidosis is a chronic inflammatory multisystem disorder of unknown etiology, associated with non-caseous granulomas.\textsuperscript{1,2} Interferon (IFN)-\textalpha is an immunomodulator used as an antiviral agent in the treatment of chronic hepatitis C virus (CHC).\textsuperscript{3} Interferon-\textalpha has been linked to pulmonary macrophage activation, a characteristic feature in sarcoidosis.\textsuperscript{4-20} Several reports in the literature have suggested an association between IFN-\textalpha with ribavirin combination therapy and sarcoidosis.\textsuperscript{21-31} We herein report a case of a 57-year-old woman with CHC who developed sarcoidosis two months after completion of a six-month IFN-\textalpha and ribavirin combination therapy and spontaneously recovered after ten months of follow-up.

\textbf{Case Presentation}

In 2007, 53-year-old Caucasian woman was diagnosed with CHC genotype 3 after routine blood analyses. Her medical history was unremarkable except for smoking a half pack of cigarettes per day and a thyroidectomy for Grave’s disease in 2001, for which she was treated with levothyroxin. She started treatment with a course of the pegylated form of IFN-\textalpha\textsubscript{2a} 180 µg once weekly (starting on the January 11 and ending on June 20, 2008) and ribavirin 1g per day (starting on January 11 and ending of June 26, 2008). Treatment was well-tolerated except for fatigue and myalgias. She was admitted to Emergency Department on August 21, 2008 for acute dyspnea, cough, painful subcutaneous nodes located in the two legs, recent weight loss, and fatigue. Body temperature was 37.3 °C (100.2 °F), heart rate was 85 beats/minute, blood pressure was 121/74 mmHg, respirations were 20/minute, and oxygen saturation was 96%. Physical examination revealed painful pretibial nodes, dry cough, inspiratory crackles on chest auscultation, chest pain with deep breaths, and enlarged liver and spleen. Chest radiograph
revealed bilateral diffuse micronodular infiltrates associated with mediastinal and hilar lymph nodes. Arterial blood gas in room air was as follows: pH 7.47 (normal range [NR] 7.38 – 7.45), PCO2 (partial pressure of carbon dioxide) 36 mm Hg (NR, 32 – 45 mmHg), PO2 (partial pressure of oxygen) 75 mm Hg (NR, 75 – 100 mm Hg), and bicarbonates 26 mmol/L (NR, 20 – 26 mmol/L). Laboratory tests including white blood cell count, blood chemistry and liver enzymes were within normal range at this time. High-resolution chest and abdominal computed tomography (CT) with contrast medium did not show pulmonary embolism but revealed several mediastinal and hilar lymph nodes and bilateral micronodular infiltrate (figure 1) in addition to enlarged liver and spleen.

She was admitted to the Internal Medicine Department for further evaluation. Clinical examination revealed a purplish skin nodule on the external edge of the lower eyelid, hepatosplenomegaly, fatigue, and moderate dyspnea. White blood cell count was slightly decreased to 3700/mm³ (NR, 4000-10000/mm³), in association with lymphopenia (830/mm³; NR, 1000 to 4000/mm³). Serological tests for Chlamydia pneumoniae, Brucellosis, and Legionella pneumophila were all negative. Mantoux test (tuberculin sensitivity test) was negative. Angiotensinconverting enzyme (ACE) level was 167 U/L (NR, 35 to 115 U/L). Calcium serum level was 2.97 mg/dL (NR, 2.20 – 2.50 mg/dL) while phosphorus serum level was within normal limits. The results of pulmonary function testing was normal, except for a distal obstruction: FEV1- 2.69 L (117% of predicted value); FEV1/FVC ratio – 0.78 (100% of predicted value); TLC – 5.43 L (105% of predicted value); FEV25 – 0.82 L per second (55% of predicted value); and diffusing lung capacity for carbon monoxide was 5.28 mmol/min/KPa (63% of predicted value). Bronchoalveolar lavage showed that CD4+ T-lymphocytes represented 61% of total
lymphocytes after centrifugation and remained negative for acid-fast and fluorescence staining for mycobacteria and fungi, respectively. No evidence of granuloma was found in transbronchial or salivary gland biopsies. Skin lesions spontaneously disappeared within three days, and therefore, no skin lesion biopsy could be performed. Eye examination was unremarkable.

After ten months of follow-up, the patient remained totally asymptomatic, and clinical examination was normal. Chest radiography returned to normal as well as white blood cell count, ACE and calcium serum levels. Normalization of mediastinal and hilar lymph nodes and resolution of bilateral micronodular infiltrate was noted on a subsequent chest CT (figure 2). Angiotensinconverting enzyme serum level normalized to 53 U/L. Pulmonary function testing showed that diffusing lung capacity for carbon monoxide was stable (64% of predicted value).

**Discussion**

Sarcoidosis is a multiple granulomatous disorder affecting the lung (more than 90% of cases), the lymphoid system (33%), liver (50% - 80%), eyes (11% - 83%) and skin (25%).\(^1,2\) Sarcoidosis has been associated with various agents whose pathogenesis involves immunological mechanisms that are only partially understood. Conversely, the immunological abnormalities of the early sarcoid reactions are well known. Sarcoid granulomas are formed in response to a persistent and probably poorly degradable antigenic stimulus or self-antigens that induce a local T-helper 1 (Th1) - type T-cell mediated immune response with an oligoclonal pattern.\(^3^2\) As a consequence of this chronic stimulation, macrophages release mediators of inflammation, locally leading to accumulation of Th1 cells at sites of ongoing inflammation and contributing to the granuloma structure.\(^1\) Histolopathologically, noncaseating epithelioid granuloma is a...
consequence of this exaggerated cellular immune response and irritation of the normal tissue architecture in affected organs by accumulation of CD4+ T lymphocytes of the Th1 type and mononuclear phagocytes.\textsuperscript{1} The immunopathology of sarcoidosis has been best characterized in cases of pulmonary disease, in which early lesions consist of an alveolitis with a high proportion of active CD4 lymphocytes.

Although the etiology of sarcoidosis remains unknown, there is a theory that it results from exposure of genetically susceptible hosts to specific environmental agents. Recent genomic and proteomic technology has emphasized the importance of host susceptibility and gene-environment interaction in the expression of the disease.\textsuperscript{33} Possible causative agents included infectious, such as viruses or mycobacteria (especially \textit{mycobacterium tuberculosis}), organic or inorganic agents.\textsuperscript{1} Hepatitis C virus itself may be a cofactor in the pathogenesis of sarcoidosis in patients receiving IFN. Indeed, hepatitis C virus may activate a Th1 immune response, and some cases of sarcoidosis diagnosed in untreated patients have been reported.\textsuperscript{6,14}

Interferon is produced in response to viral, bacterial, parasitic, or tumor antigens. Interferon-α is widely used in the treatment of CHC because of its anti-viral effects.\textsuperscript{3} Pegylated IFN-α and ribavirin were found to be superior to all previously proposed therapeutic regimens for sustained eradication of the hepatitis C virus.\textsuperscript{34,35} Experimental studies have shown that IFN-α is involved in the activation of T lymphocytes and subsequent production of various cytokines.\textsuperscript{36} Shiomi et al\textsuperscript{37} showed that in patients treated with IFN-α for CHC and examined with Gallium-citrate scanning, there was a significant increase in radionuclide uptake in the lung after therapy, suggesting subclinical inflammatory process in asymptomatic individuals. The role of IFN-α in
inducing predominant Th1 immune response is therefore possible. Ribavirin may also enhance Th1 response by increasing production of IL-12, IFN-γ, and TNF-α mRNA and proteins, and by decreasing the Th2 response. Consequently, enhanced Th1 immune reaction induced by the combined therapy may trigger granulomatous reactions more frequently than IFN-α monotherapy. This may explain why only ten cases of IFN-α-induced sarcoidosis were published between 1993 and 1999; while in the last seven years, coinciding with the generalized use of combined therapy, the number of cases reported has increased four-fold.

To our knowledge, the first association between sarcoidosis and CHC was reported in 1993 by Blum et al and was directly related to the onset of IFN-α therapy. Since then, the number of cases reported annually has increased significantly, suggesting a closer association than previously suspected. The relationship between IFN-α administration and the development of sarcoidosis seemed to be clear in nearly all cases. More than 70 cases of IFN-α-induced sarcoidosis were reported in the literature. Ramos-Casals et al analyzed the relationship between sarcoidosis and CHC. This retrospective study described the clinical characteristics, patterns of association, and the role of antiviral therapy in 68 patients. In two-thirds of the patients described in this study, sarcoidosis was triggered during the first six months of antiviral therapy, and occurred with IFN-α monotherapy in 20 cases and combined therapy with IFN-α and ribavirin in 30 cases. In eight patients, initiation of antiviral therapy for CHC reactivated pre-existing sarcoidosis. The authors suggested a possible additional role for ribavirin. Indeed, in ten of 12 patients who received IFN-α before developing sarcoidosis, the granulomatous lesion appeared during a second course of treatment with IFN and ribavirin, and not earlier with IFN alone.
The appropriate treatment of sarcoidosis has not been well-defined by the ATS/ERS/WASOG Committee (American Thoracic Society/ European Respiratory Society/ World Association for Sarcoidosis and Other Granulomatous Disorders).\textsuperscript{1,2} Corticosteroids can reverse the granulomatous process.\textsuperscript{41} A systematic review of the effects of corticosteroids treatment in patients provides evidence that these agents in oral or inhaled forms may lead to improvement in radiographic appearance and pulmonary function.\textsuperscript{42} The natural history of sarcoidosis is highly variable, with a tendency to wax and wane, either spontaneously or in response to therapy. Spontaneous remission may occur in nearly two-thirds of patients.\textsuperscript{2} In the case of drug-induced sarcoidosis as described by Ramos-Casals et al,\textsuperscript{6} specific therapy for sarcoidosis was started in only half of the patients (21/42 cases specified), including oral corticosteroids in 17 cases. However, improvement or remission was clearly related to discontinuation of antiviral therapy.

Although no evidence of granuloma was found in transbronchial or salivary gland biopsies, our patient had typical features of sarcoidosis, i.e., fever, spontaneously resolving purplish skin nodule in external edge lower eyelid, chest radiography and CT images (figure 1), hypercalcemia, high CD4+ T-lymphocytes in bronchoalveolar lavage, and significantly elevated ACE. Therefore, based on compatible clinical, biological and radiologic findings and according to the recommendations of the ATS/ERS/WASOG,\textsuperscript{1,2} the diagnosis of sarcoidosis was considered in our patient, despite the lack of histological confirmation. Transbronchial lung biopsy is the recommended procedure in most cases, but its diagnostic value depends largely on the experience of the operator, ranging from 40\% to > 90\%.\textsuperscript{1} Based on the recommendations of the ATS/ERS/WASOG, a classic Löfgren’s syndrome may not require biopsy proof if resolution of disease is rapid and spontaneous,\textsuperscript{1} which was the case in our patient. In our case, we
hypothesized that the antiviral therapy could induce sarcoidosis, based on the pathophysiological mechanisms reviewed in the literature. Immune memory could be implicated for such a hypothesis. Indeed, the current observation is interesting due to the time elapsed between symptom occurrence and antiviral therapy withdrawal. To the best of our knowledge, this will be the first case of sarcoidosis occurring several months after the end of antiviral therapy. It is unclear whether the combination therapy actually precipitated sarcoidosis de novo or even unmasked a previously subclinical case, although our patient had no clinical findings to suggest pre-existing sarcoidosis. However, a range of 30% to 60% of reported cases of sarcoidosis are asymptomatic and have been discovered by the presence of characteristic findings on routine chest radiography. As suggested by Ramos-Casals et al, in addition to the accurate evaluation of the treatment-related adverse effects, chest radiograph upon starting antiviral therapy and subsequent specific follow-up may be proposed, although no risk factor for IFN-α and/or ribavirin-induced granulomatosis has been yet identified to the best of our knowledge. Furthermore, serum calcitriol and ACE levels could be used as screening tests for drug-induced macrophage activation in future patients receiving IFN-α. Spontaneous rapid resolution of symptoms and the lack of severe clinical manifestation explained the lack of systemic steroid requirement in our patient. The prognosis for IFN-α-induced sarcoidosis seems to be good when the medication is discontinued, which was the case in the current observation.

In conclusion, inflammatory granulomatosis, especially sarcoidosis, may appear during, but also upon completion of, a pegylated-IFN-α2a and ribavirin combination therapy that may spontaneously disappear. Future studies may be helpful to determine predictive factors like
definition of genetic risk profiles associated with this immunological adverse event and those associated with its spontaneous resolution in some cases.
References


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**Figure Legends:**

**Figure 1.** (a) High-resolution chest CT with contrast medium demonstrating several enlarged mediastinal and hilar lymph nodes. (b) High-resolution chest CT with contrast medium demonstrating bilateral micronodular infiltrate.
Figure 2. (a) After ten months follow-up, high-resolution chest CT with contrast medium demonstrating complete normalization of mediastinal and hilar lymph nodes. (b) After ten months follow-up, high-resolution chest CT with contrast medium demonstrating resolution of bilateral micronodular infiltrate.