CASE REPORT

Sarcoidosis after treatment with interferon-α: A case series and review of the literature

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Summary
Recombinant interferon-α (rINF-α) is an immunomodulator used in the treatment of various conditions, including viral infections and malignancies. The use of rINF-α has been associated with the development of sarcoidosis in recent case reports. In this series, we report the incidence of sarcoidosis in recipients of rINF-α for hepatitis C viral (HCV) infection at our institution. We also review the 57 additional cases of sarcoidosis associated with rINF-α described in the literature, including clinical presentation, radiographic findings, management, and outcomes, and discuss the potential mechanisms by which rINF-α may lead to the development of sarcoidosis.

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Introduction
Recombinant interferon-α (rINF-α) is an immunomodulator used in the treatment of various conditions, including viral infections and malignancies. The inclusion of this agent in the treatment regimens of such diseases, and of viral hepatitis in particular, has been associated with improved outcomes, though also with significant side effects. Recent case reports describe the onset of systemic sarcoidosis in patients managed with r-INF-α for the above conditions. In this case series, we report the incidence of sarcoidosis in recipients of rINF-α for hepatitis C viral (HCV) infection at our institution. We also review the 57 additional cases of sarcoidosis associated with rINF-α described in the English literature, including clinical presentation, radiographic findings, management, and outcomes, and discuss the potential mechanisms by which rINF-α may lead to the development of sarcoidosis.

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Methods
Case series
Of all individuals treated for chronic active HCV infection at University Hospital of Bexar County, TX, and the Audie L. Murphy Veterans’ Administration Hospital in San Antonio, TX between 6/1/02 and 6/1/05, we included in our subject cohort any patients referred to specialists by their primary or GI physicians for potential manifestations of sarcoidosis. We collected available data for these patients relating to clinical presentation, laboratory, spirometric, and radiographic evaluations, as well as diagnostic and therapeutic interventions, for this report. Based upon these findings, we calculated the incidence of sarcoidosis in our population of patients who received rINF-α, and compared this incidence to those HCV patients never exposed to rINF-α.

Literature review
We performed a Medline search and cross-reference of “Interferon” and “Sarcoidosis” to identify case reports of an association between these disorders in the literature. Reports of sarcoidosis development in association with rINF-α with an abstract or full text available in English were reviewed, and available data regarding clinical presentation, radiographic findings, management, and outcomes are reported here.

Statistics
A two-sided comparison of population proportions was used to compare the incidence of sarcoidosis in patients with HCV at our institutions that were exposed to rINF-α with that of those who never received this medication.

Results
Of 667 patients treated with rINF-α for HCV at our institution, we identified three cases of biopsy-proven sarcoidosis (incidence 0.44%). Two patients were African American (2/63, incidence 3.17%) and one Caucasian (1/267, incidence 0.37%). None of the 332 Hispanic or 5 Asian patients who received rINF-α was identified as suffering from sarcoidosis. No cases of sarcoidosis were observed among 3862 patients with HCV who never received rINF (P<0.0004.) Of this group, 50% were Hispanic, 40% Caucasian, and 10% African American. Our three cases are briefly described here.

Case 1
A 54-year-old African American male, diagnosed with chronic, active HCV by liver biopsy, was initiated on INF-α plus ribavirin. Two months later, he developed a cough productive of clear sputum and dyspnea on exertion. Physical examination revealed no adenopathy and lungs were clear to auscultation.

Pulmonary function tests demonstrated mild obstruction, normal lung volumes, and normal diffusing capacity. Chest imaging showed a diffuse nodular infiltrate, with minimal bilateral hilar and mediastinal lymphadenopathy (Fig. 1). No evidence of sarcoidosis was seen on review of the patient’s liver biopsy. The patient underwent fiberoptic bronchoscopy with trans-bronchial biopsy, which revealed non-necrotizing sarcoidal granulomas with many multinucleated giant cells (Fig. 2). Cultures showed no growth. The patient’s rINF-α was

Figure 1 Chest CT of patient 1 demonstrating diffuse parenchymal nodularity and hilar adenopathy.
discontinued, with resolution of symptoms and radiographic findings.

**Case 2**

A 54-year-old African American male was diagnosed with chronic active HCV by liver biopsy and started on pegylated INF-$\alpha$ and ribavirin. Six months later, he developed dyspnea and a cough productive of clear sputum. One month subsequent to this, he complained of pain and swelling at a tattoo site. Physical examination showed no palpable lymphadenopathy and lungs were clear to auscultation. Skin exam was notable for eczematous patches and plaques at the patient’s tattoo site.

On pulmonary function testing, the patient had mild obstruction with normal lung volumes and diffusing capacity. Chest radiography showed innumerable tiny interstitial nodules throughout the lungs bilaterally, bilateral symmetric hilar adenopathy, and multiple sub centimeter lymph nodes throughout the mediastinum. A skin biopsy revealed sarcoidal type non-necrotizing granulomas in the subcutaneous tissue (Fig. 2). Staining revealed no organisms. The patient’s anti-viral therapy was discontinued, with resolution of skin findings 2 months later and improvement in pulmonary symptoms and radiographic findings by 6 months.

**Case 3**

A 44-year-old Caucasian female was diagnosed with chronic active HCV by liver biopsy and initiated on rINF-$\alpha$ and ribavirin. One month later, she developed a rash. Physical exam revealed no evidence of lymphadenopathy and lungs were clear to auscultation. Skin exam was notable for subcutaneous nodules over the upper extremities. Chest radiography showed sub centimeter hilar and mediastinal lymphadenopathy. The patient underwent excision of a subcutaneous nodule from her right upper extremity, which showed non-casseeating granulomata with absence of growth on cultures. Her antiviral-therapy was discontinued, with initial improvement in her symptoms. Symptoms recurred, however, 6 months after discontinuation of rINF-$\alpha$. Her management is ongoing.

**Discussion**

Sixty cases of sarcoid development after the institution of rINF-$\alpha$ therapy have been reported in the English literature, including the individuals described above. The mean age of patients was 49.8 years (range 26–67). The race and gender of the subjects was not commonly reported. While the majority of individuals (52/60) received therapy for HCV, sarcoidosis has also developed in association with the management of Hepatitis B infection, lymphoproliferative malignancies and other hematologic conditions.

The mean time to onset of symptoms was 11.4 months (range 1–60 months). A number of patients experienced no symptoms of sarcoidosis during initial treatment, but developed symptoms during repeated courses of INF-$\alpha$. In some instances, symptoms developed from as early as one week to as late as 3 years after discontinuation of the drug.

The most commonly affected organs included skin and lungs, though many other organ systems have also been involved (see Table 1). Other manifestations of disease included erythema nodose, hypercalcemia and LoFgren’s Syndrome.

The majority of patients underwent both chest X-ray and CT scanning during their evaluations. Lymphadenopathy was found most often (24/46 patients), either alone or in combination with...
promoting granuloma formation. Exogenous INF-α has been implicated in the alteration of lymphocyte capacity, and/or restriction either alone or in combination. Diagnosis was most often accomplished via skin or lung biopsies. Lymph node biopsy and liver biopsy were each utilized in six and four cases, respectively. The most common method of management was discontinuation of therapy, either alone or in combination with systemic corticosteroids. Two patients were treated with dose reduction and three required no interventions. The majority of patients experienced resolution or improvement in symptoms; however, seven suffered persistent or relapsing courses.

The mechanisms by which cytokine production influences granuloma formation in systemic sarcoidosis are currently under investigation. Sarcoidosis is thought to result from a cell mediated T helper 1 response. IL-2, IL-12, and IL-18 levels are increased in broncho-alveolar lavage (BAL) fluid of patients with sarcoidosis, supporting the contention that a Th1 response is involved with sarcoid pathogenesis. Inui et al. demonstrated that stimulation of BAL fluid cells isolated from patients with sarcoidosis led to increased IFN-γ production and an increased ratio of IFN-γ/IL-4 from CD-4 cells compared to normal controls.

INF-α may increase IFN-γ and IL-2 levels, thus promoting granuloma formation. Exogenous INF-α has been implicated in the alteration of lymphocyte profiles in BAL fluid. Furthermore, Akahoshi et al. demonstrated that a particular single nucleotide polymorphism in the INF-α gene led to increased INF-α levels and an increased incidence of sarcoidosis. Thus, exposure to exogenous INF-α could theoretically contribute to the development of sarcoidosis by its effects on cytokines that stimulate the T helper 1 pathway.

Our study may underestimate the incidence of sarcoidosis in both the interferon exposed and unexposed groups, as only individuals referred to specialists and with biopsy proven sarcoidosis were included in our analysis. In addition, while our review suggests that exposure to rINF-α may contribute to the development of sarcoidosis in patients with HCV, the severity of their underlying liver disease and concomitant medication use could be contributing factors. A conclusive association cannot be established by these reports, however. Prior studies have suggested that HCV infection in itself may increase the risk of sarcoidosis, independent of therapy. The threefold increased incidence of sarcoidosis in our African American population treated with rINF-α as compared to those never exposed to the drug argues against infection with HCV as the sole etiology for the development of sarcoidosis. Moreover, most patients in our search stabilized or improved after rINF-α was discontinued, despite continued active HCV infection.

Our case series reflects the characteristics of sarcoidosis that seem to be typical in association with rINF-α therapy, but that differ from other forms of systemic sarcoid. Diffuse nodular parenchymal abnormalities, while uncommonly seen in sarcoid patients in general, were observed in two of our three patients and in one third of cases in our literature review. In addition, the relatively mild course of disease and rapid response to discontinuation of therapy observed in our case series and in the majority of cases reported is in contradiction to the natural history of the disease in general. Further study regarding the potential contribution of HCV infection and its therapy, as well as the genetic predisposition in this population, warrants further study.

### References


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<th>Table 1</th>
<th>rINF-α.</th>
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<tr>
<td>Organ</td>
<td>Number of cases</td>
</tr>
<tr>
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<td>Liver</td>
<td>5</td>
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CNS: central nervous system; PNS: peripheral nervous system.