Sarcoidosis Associated With Pegylated Interferon Alfa and Ribavirin Treatment for Chronic Hepatitis C

A Case Report and Review of the Literature

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Background: At least 2.7 million Americans are infected with chronic hepatitis C. An increasing number are treated with interferon alfa plus ribavirin regimens. Not surprisingly, this immune stimulation is associated with the development of autoimmune and cutaneous diseases. Several cases of sarcoidosis have been reported with hepatitis C treatment, most recently in association with pegylated interferon alfa plus ribavirin. Systemic manifestations of sarcoidosis are usually treated with oral steroids, which unfortunately often increase the hepatitis C viral load. Thus, it is important to ascertain whether systemic corticosteroids are required to treat interferon alfa–associated sarcoidosis.

Observations: We report the third case of cutaneous sarcoidosis in association with pegylated interferon alfa plus ribavirin treatment. Our patient had both cutaneous and pulmonary involvement, which has been spontaneously resolving since his treatment regimen was completed. In addition, we review the 12 previously reported cases of cutaneous sarcoidosis that occurred in patients undergoing hepatitis C treatment with interferon alfa.

Conclusions: As the number of patients being treated with interferon alfa and ribavirin for hepatitis C increases, it is essential that dermatologists recognize the association of this treatment with sarcoidosis, because skin lesions may provide the first clue to diagnosis. Development of sarcoidosis may relate to hepatitis C as a possible antigenic trigger in the presence of an enhanced helper T cells type 1 response from treatment. Sarcoidosis with skin lesions in patients undergoing hepatitis C treatment often follows a benign course, and interferon alfa therapy may sometimes be continued with resolution of sarcoidosis occurring spontaneously or within a few months of completing treatment. Cautious use of systemic corticosteroids is warranted given their adverse effects on hepatitis C viral loads.

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CHRONIC HEPATITIS C AFFECTS AT LEAST 170 MILLION PEOPLE WORLDWIDE AND IS THE LEADING INDICATION FOR LIVER TRANSPLANTATION IN EUROPE AND THE UNITED STATES.1 IN MANY PATIENTS, IMMUNOMODULATORY TREATMENT REGIMENS THAT USE INTERFERON ALFA ARE USEFUL IN ERADICATING THE VIRUS. UP TO 20% OF PATIENTS REPORT ADVERSE CUTANEOUS EVENTS TO INTERFERON ALFA.2 WE REPORT THE THIRD CASE OF CUTANEOUS SARCOIDOSIS ASSOCIATED WITH COMBINATION PEGYLATED INTERFERON ALFA AND RIBAVIRIN TREATMENT FOR HEPATITIS C. ALSO INCLUDED IS A LITERATURE REVIEW OF ALL CASES OF CUTANEOUS SARCOIDOSIS THAT OCCURRED IN ASSOCIATION WITH INTERFERON ALFA TREATMENT FOR HEPATITIS C.

REPORT OF A CASE

A 63-year-old Hispanic man with no previous history of sarcoidosis received peginterferon alfa-2a, 135 µg injected subcutaneously once weekly, and ribavirin, 400 mg orally twice daily, for chronic hepatitis C (genotype 2) infection. He was previously untreated and responded well, with an undetectable viral load and improvement in liver function tests at 24 weeks of treatment. Six months after therapy was instituted, he noted the gradual and progressive appearance of asymptomatic skin lesions on his forehead, scalp, and extremities. At the same time, his review of systems was notable for an occasional cough productive of clear sputum. He had no other pulmonary symptoms and was able to hike several miles and play racquetball regularly.

Four months after noting the first skin lesions, the patient presented to the San Francisco Veterans Affairs Dermatology Clinic (San Francisco, Calif), with multiple violaceous dermal papules that coalesced into plaques on his right knee and the bilateral aspects of his elbows.

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He also had pink dermal papules arising in 2 tattoos and several yellow indurated dermal nodules on his brow line, forehead, and scalp. No lymphadenopathy was apparent.

Skin biopsies were performed on a papule from the right elbow and a forehead nodule. Histopathologic examination of both specimens revealed dermal granuloma composed of epithelioid histiocytes and multinucleate giant cells with sparse peripheral lymphocytes (Figure 2). Special stains for bacterial, fungal, and mycobacterial organisms produced negative results.

Concurrently, the serum angiotensin-converting enzyme level was found to be 96 U/L (reference range, 9-67 U/L). The serum calcium level was normal. The patient had undergone computed tomography of the chest 7 months after starting his hepatitis therapy, which revealed multiple subcentimeter lymph nodes in the para-tracheal and pretracheal regions and scattered 5- to 9-mm bilateral lung nodules. The results of an ophthalmologic examination were unremarkable.

At the time of diagnosis of sarcoidosis, the patient had only 3 weeks left in his 48-week course of hepatitis treatment. Because he had no significant pulmonary symptoms except for mild cough and no other evidence of systemic sarcoidosis, his course of peginterferon alfa-2a and ribavirin was completed. Gradual resolution of his cutaneous lesions followed. Ten weeks later, marked clinical improvement was noted, with a decrease in size and fading of all skin lesions. A follow-up chest computed tomographic scan 8 weeks after treatment cessation revealed resolution of the pulmonary nodules and a decrease in size of multiple mediastinal lymph nodes.

More than 170 million people worldwide, including approximately 2.4% of the US population, are infected with chronic hepatitis C. Current antiviral treatments are effective in eradicating the virus in up to 60% of patients. Several treatment regimens have been used, including interferon alfa monotherapy, interferon alfa plus ribavirin, and most recently peginterferon alfa with or without ribavirin. Pegylated interferon alfa is synthesized by adding a polyethylene glycol molecule to the standard interferon structure to produce a biologically active molecule with more sustained absorption and a longer half-life, allowing convenient once-weekly dosing. Pegylated interferon alfa plus ribavirin was found to be superior to all other regimens for sustained eradication of the hepatitis C virus, especially in individuals with more resistant viral genotypes 1, 4, 5, and 6.

Adverse effects of hepatitis C treatment are common, with similar profiles among the various treatment regimens. Fatigue, headache, fever, and myalgias top the list of adverse effects and occur in approximately 40% to 55% of patients. Cutaneous events, including pruritus and rashes, are reported in up to 20%. An increasingly recognized adverse effect of interferon alfa therapy for hepatitis C is sarcoidosis.

Sarcoidosis is a systemic disease of unknown etiology characterized by noncaseating epitheloid granuloma formation that affects almost any organ system. The lungs, liver, lymph nodes, eyes, and skin are commonly involved. Although the exact cause of sarcoidosis remains a mystery, it is thought to represent an exaggerated immune response to unknown antigenic stimuli. Tuberculosis, other infectious agents, environmental stimuli, and malignancies have all been reported in association with the development of sarcoidosis. However, no reported link exists between untreated hepatitis C infection and sarcoidosis.

In sarcoidosis, there appears to be a predominance of helper T cells type 1 (Th1) and interleukin (IL) 2. Local macrophages are also activated and produce IL-1, IL-12, and interferon gamma. Helper Th2 cells type 2 (Th2) lymphocytes are relatively inactive in the granulomas, and there are proportionately low levels of Th2-associated cytokines. Interferon alfa is successful in treating infectious diseases because of its immunomodulating effects. In vitro, interferon alfa causes Th cells to produce large amounts of interferon gamma and limited amounts of IL-4 and IL-5, suggesting that interferon alfa favors the development and enhancement of Th1-mediated responses. This enhancement of...
cell-mediated immunity in the presence of an antigenic stimulus such as the hepatitis C virus may be partially responsible for the development of sarcoidosis in patients treated with interferon alfa.

Abdi et al\textsuperscript{9} described the first case of pulmonary sarcoidosis in a patient who received interferon beta for renal cell cancer in 1987. Since then, numerous cases have been published, suggesting a relationship between sarcoidosis and interferon treatment in patients with a variety of diseases, including renal cell carcinoma, hematologic malignancies, and hepatitis. More than 25 cases of sarcoidosis that occurred in association with interferon alfa treatment for chronic hepatitis C have been reported. A review of the English literature found 13 cases (including the current one) in which the sarcoidal manifestations included cutaneous lesions.\textsuperscript{10-13} Details of these cases are summarized in the Table.

Six patients had only cutaneous involvement. One patient had cutaneous plus liver involvement discovered on an incidental protocol biopsy specimen.\textsuperscript{17} Many patients, including our case, had negative ocular examination results. All but 1 had an elevated angiotensin-converting enzyme level. Only 1 patient had a possible previous history of sarcoidosis.\textsuperscript{13} The mean time to onset of disease from the start of interferon alfa treatment was 4 months. Of note, responder status to treatment was essentially equal in those cases in which it was specified (4 responders vs 5 nonresponders) and did not correlate with the mean time to onset. Men and women were equally affected. In the 5 cases in which race was specified, 3 patients were white, 1 was African American, and our patient was Hispanic. Hepatitis C viral genotype 1a occurred in 3 patients, with genotypes 3a and 2 specified in 2 others.

Nine of the cases occurred in patients who received a combination treatment of interferon alfa or pegylated interferon alfa and ribavirin. In 3 of these cases, patients had previously been treated with interferon alfa only without any manifestations of sarcoidosis. This suggests that the combination of interferon alfa and ribavirin further modifies or enhances the immune response in a way that predisposes the patient to sarcoidosis. Although the exact mechanism of ribavirin in treating hepatitis C is unknown, a recent study\textsuperscript{19} showed that it also enhances Th1 responses when applied to T cells in vitro. This may explain why combination therapy with interferon alfa and ribavirin is more efficacious in treating hepatitis C virus and why it also may further predispose patients to sarcoidosis and other autoimmune diseases. No cases of sarcoidosis that occurred with ribavirin-only treatment have been reported.

Most patients with interferon alfa–associated sarcoidosis had resolution of their disease without immunosuppressive treatment. In several cases, interferon alfa treatment was discontinued because of either sarcoidosis or hepatitis nonresponder status. Subsequent resolution of sarcoidosis within months was the rule. In 4 of the cases, the treatment regimen was not modified and the sarcoidosis resolved several months later, either during or after the completion of treatment. Two patients were treated with oral corticosteroids with rapid resolution. Although our patient had radiologic evidence of pulmo-

### Table. Cases of Cutaneous Sarcoidosis Associated With Interferon Alfa Treatment for Chronic Hepatitis C

<table>
<thead>
<tr>
<th>Source</th>
<th>Age, y/</th>
<th>Sex</th>
<th>Treatment</th>
<th>Prior Interferon Alfa Only</th>
<th>Onset, mo</th>
<th>Findings</th>
<th>ACE Level, U/L</th>
<th>Treatment</th>
<th>Follow-up and Resolution</th>
<th>Responder Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffmann et al,\textsuperscript{16} 1998</td>
<td>39/M</td>
<td>Interferon alfa</td>
<td>No</td>
<td>5</td>
<td>C, P</td>
<td>88</td>
<td>Discontinued</td>
<td>5-mo Resolution</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Eberein-König et al,\textsuperscript{11} 1999</td>
<td>60/F</td>
<td>Interferon alfa</td>
<td>No</td>
<td>4</td>
<td>C</td>
<td>108</td>
<td>Decreased interferon alfa</td>
<td>Clinical improvement</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Neglia et al,\textsuperscript{17} 2001</td>
<td>50/F</td>
<td>Interferon alfa</td>
<td>No</td>
<td>3</td>
<td>C</td>
<td>56</td>
<td>Discontinued</td>
<td>2-mo Resolution</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Pérez-Álvarez et al,\textsuperscript{13} 2002</td>
<td>38/M</td>
<td>Interferon alfa, ribavirin, amantadine</td>
<td>Yes</td>
<td>3</td>
<td>C, P</td>
<td>108</td>
<td>Discontinued; oral corticosteroids</td>
<td>3-mo Resolution</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Cogrel et al,\textsuperscript{14} 2002</td>
<td>44/F</td>
<td>Interferon alfa, ribavirin</td>
<td>Yes</td>
<td>3</td>
<td>C, P</td>
<td>94</td>
<td>NA</td>
<td>6-mo Resolution</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Wendling et al,\textsuperscript{15} 2002</td>
<td>30/F</td>
<td>Interferon alfa, ribavirin</td>
<td>No</td>
<td>4</td>
<td>C, P</td>
<td>128</td>
<td>No change in treatment</td>
<td>3-mo Resolution</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Navras et al,\textsuperscript{16} 2002</td>
<td>50/F</td>
<td>Interferon alfa, ribavirin</td>
<td>No</td>
<td>3</td>
<td>C</td>
<td>48 (normal)</td>
<td>No change in treatment</td>
<td>Resolution, time unspecified</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gitlin,\textsuperscript{17} 2002</td>
<td>49/M</td>
<td>Interferon alfa, ribavirin</td>
<td>No</td>
<td>4</td>
<td>C, L</td>
<td>120</td>
<td>Discontinued</td>
<td>1-y Resolution</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Rogers et al,\textsuperscript{18} 2004</td>
<td>52/M</td>
<td>Interferon alfa, ribavirin</td>
<td>No</td>
<td>5</td>
<td>C</td>
<td>152</td>
<td>Discontinued</td>
<td>5-mo Resolution</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Current case</td>
<td>63/M</td>
<td>Peginterferon alfa, ribavirin</td>
<td>No</td>
<td>6</td>
<td>C, P</td>
<td>96</td>
<td>No change in treatment</td>
<td>2.5-mo Resolution after treatment completion</td>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

Source abbreviations: ACE, angiotensin-converting enzyme; C, cutaneous sarcoidosis; L, hepatic sarcoidosis; NA, not available; NR, treatment nonresponder; NS, treatment response not specified; P, pulmonary sarcoidosis; R, treatment responder.
nary involvement that resolved after his interferon alfa treatment was completed, he did not experience significant pulmonary compromise and continued his daily activities, including hiking and racquetball.

Sarcoidosis with skin lesions that occurs in patients undergoing interferon alfa treatment for hepatitis C often follows a benign course, and hepatitis treatment may possibly be continued with close monitoring for systemic problems such as pulmonary compromise. On the basis of the reported cases, interferon alfa–associated sarcoidosis with cutaneous involvement can be expected to resolve within approximately 6 months of treatment discontinuation, if not sooner. Several cases resolved spontaneously despite the continuation of interferon alfa and ribavirin treatment. Steroids, which are the main treatment for systemic sarcoidosis, increase the hepatitis C viral load both in vitro and in vivo. Physicians should thus exert caution in treating interferon alfa–associated sarcoidosis with systemic corticosteroids.

Our case is the third reported case of cutaneous sarcoidosis that occurred with peginterferon alfa and ribavirin treatment. As more patients are treated with this regimen because of greater efficacy and convenience of administration, predisposition to sarcoidosis will likely prove to be an increasingly recognized adverse effect. As in other cases of sarcoidosis, the skin is a commonly affected organ. Because symptoms of sarcoidosis such as fever, fatigue, and anorexia are often nonspecific and similar to the frequent adverse effects associated with hepatitis C treatment, the dermatologic examination can often provide helpful diagnostic clues and skin biopsy can yield rapid diagnosis.

Dermatologists and other physicians should be aware of the enhanced potential for cutaneous and systemic sarcoidosis in patients undergoing interferon alfa treatment for hepatitis C. In cases with skin lesions, interferon alfa treatment may sometimes be continued and oral corticosteroids should be used judiciously in what is often a mild sarcoidal disease course. Further investigation into the possible association of hepatitis C as an antigenic trigger coupled with enhanced Th1 immune responses related to interferon alfa treatment may contribute to understanding the etiology and pathogenesis of what remains a mysterious disease.

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REFERENCES