Severe, Generalized Nummular Eczema Secondary to Interferon Alfa-2b Plus Ribavirin Combination Therapy in a Patient With Chronic Hepatitis C Virus Infection

Megan M. Moore, BA; David J. Elpern, MD; Daniel J. Carter, MD

**Background:** With increasing rates of hepatitis C virus infection and diagnosis, more patients are being treated with interferon alfa-2b plus ribavirin therapy. Cutaneous side effects to combination therapy are common and may limit treatment. There are few previous case reports of generalized eczematous dermatoses occurring after combination therapy for hepatitis C virus, none in a North American patient, and none of this severity or recalcitrance.

**Observations:** A man with chronic hepatitis C virus infection and no history of atopy developed severe, recalcitrant nummular eczema secondary to interferon alfa-2b plus ribavirin combination therapy. The cutaneous side effect was more severe than in previously reported cases and did not remit on discontinuation of therapy.

**Conclusions:** Greater awareness of the range of dermatologic responses to interferon alfa-2b plus ribavirin therapy may lead to improved surveillance for and treatment of these side effects. Investigating the underlying pathologic mechanisms may ultimately allow for a greater understanding of the immunomodulatory effects of this therapy in the setting of chronic hepatitis C virus infection.

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**REPORT OF A CASE**

A 50-year-old white male had chronic HCV infection diagnosed in 1993. He had been treated with interferon alfa for 4 months in 1997 without cutaneous side effects, but his condition relapsed and treatment was started with a combination of ribavirin capsules, 600 mg orally twice daily, and recombinant interferon alfa-2b, 3 million IU injected subcutaneously 3 times a week (Rebetron; Schering-Plough, Memphis, Tenn) in fall 2001.

Four months after beginning combination therapy, the patient presented to the dermatologist for evaluation and treatment of intractable pruritus. He had experienced mild pruritus, mostly of the back, throughout the treatment, but the onset of severe itching and dermatitis had begun a week before his dermatologic visit. At that time, he exhibited marked excoriations on the arms, back, and face, with areas of honey-colored crusting.

The eruption started at the injection sites on the anterior part of the thighs but began to generalize after a few days. Within 2 weeks of his first dermatologic visit, he developed an impressive eruption consisting of annular, erythematous, crusted plaques that began at the injection sites on the thighs and spread across the arms, torso, and face (Figure 1 and Figure 2). Treatment with ribavirin and interferon alfa-2b was stopped.

There was no history of previous dermatologic disease or atopy. There was no family history of dermatologic disease.

At the time of initial presentation, the hemogram showed a white blood cell count of $3.1 \times 10^9/\mu L$ with a normal differential count, a hemoglobin level of 10.9 g/dL (hematocrit, 30.7%), 3.9% reticulocytes, and a normal platelet count. Results of liver function tests were normal except for an elevated total bilirubin level of 1.93 mg/dL (33 µmol/L) with an indirect bilirubin level of 1.64 mg/dL (28 µmol/L).

A biopsy specimen showed mild epidermal hyperplasia with marked spongiosis and a mixed inflammatory cell infiltrate in the superficial dermis and epidermis. There was focal parakeratosis and scale crust. The pathologic findings were most consistent with a subacute eczematous dermatitis (Figure 3 and Figure 4).

From Harvard Medical School, Boston, Mass (Ms Moore); The Skin Clinic, Williamstown, Mass (Dr Elpern); and Berkshire Medical Center, Pittsfield, Mass (Dr Carter). The authors have no relevant financial interest in this article.
After consultation with his gastroenterologist, the patient began treatment with prednisone, 20 mg 3 times daily with a 3-week taper and 0.05% betamethasone dipropionate ointment twice daily to the elevated plaques. There was marked improvement of the dermatitis, but the patient was unable to taper the prednisone without recurrence of the eruption and pruritus. The thigh injection sites remained clear and were spared with each recurrence.

Six months after his initial presentation, the patient's condition was maintained with essentially clear skin with prednisone, 5 mg/d, and topical 0.05% betamethasone dipropionate ointment as needed. He continued to taper the prednisone by 1 mg every 2 weeks.

COMMENT

Combination therapy with interferon alfa-2b plus ribavirin for 24 to 48 weeks has been investigated as an effective initial therapy for patients with chronic hepatitis C, with up to 40% of patients achieving a sustained virologic response.1-2 Although peginterferon alfa-2a plus ribavirin has recently been shown to be superior to interferon alfa-2b plus ribavirin in inducing a sustained virologic response,3 interferon alfa-2b is still in use. Side effects are similar and common with both regimens, are often severe, and are frequently limit therapy.

Dermatologic side effects from these therapies are common. Generalized cutaneous side effects of interferon alfa-2b therapies have been reported as rash, alopecia, dry skin, excessive sweating, acne, nail disorders, epidermal necrolysis, photosensitivity, skin discoloration, and exfoliative dermatitis.4-5 A wide variety of injection-site reactions, including pyoderma gangrenosum,6 leukocytoclastic vasculitis,7 interface dermatitis,8 dermal hypersensitivity,9 necrotizing ulcerations,10-12 and suppurative and granulomatous dermatitis13 have been reported. Ribavirin has been associated with pruritus4-14 and photoallergic eczematous reactions.15 Several studies have shown an increase in cutaneous side effects in patients receiving combination therapy vs interferon monotherapy16-19; however, few describe the types of dermatoses in detail.

There are few studies in the North American literature. Our patient’s dermatologic side effect has not been reported in a North American patient, to our knowledge, and may be the first reported case of this severity and persistence.

Manjon-Haces et al20 described a series of 210 patients in Spain with HCV undergoing treatment with interferon alfa-2b plus ribavirin. Twenty-seven patients (13%) had significant cutaneous reactions, including localized eczematous lesions in 14, and generalized eczematous lesions in only 2. In 7 of the patients with ec-
zematous lesions, histopathologic studies were performed and showed superficial perivascular dermatitis with spongiosis. Unlike our patient, none of these patients modified their treatment because of their lesions, and all lesions resolved completely on termination of therapy.

Sookoian et al\textsuperscript{21} reported cutaneous reactions in 11 (33\%) of 33 patients in Argentina with chronic HCV receiving interferon alfa (2a or 2b not specified) plus ribavirin combination therapy vs 2 (6\%) of 35 of those receiving interferon alone. Three of the patients in the combination therapy group developed “eczema,” with histologic diagnoses of “subacute psoriasiform dermatitis,” “eczema psoriasiform,” and “eczema.” The lesions were limited to the arms and/or legs, unlike the generalized presentation in our patient. Only 1 of the 11 patients with cutaneous adverse effects had to discontinue treatment temporarily because of these effects.

Berger et al\textsuperscript{22} reported 4 cases of eczema in atopic patients in France with chronic HCV receiving interferon alfa-2a or alfa-2b therapy. Three of these patients also took ribavirin, and all had a history of certain or possible atopy. One patient receiving combination therapy had nummular eczema. Two of the patients receiving combination therapy had received interferon monotherapy previously without adverse dermatologic effects. In all these cases, the lesions began at the injection site and, unlike in our patient, resolved with termination of therapy. Patch, prick, and intradermal skin tests were negative, including testing for interferon alfa reaction. Delayed-type hypersensitivity with a positive patch test to interferon alfa-2c and an enzyme-linked immunosorbent assay positive for anti-interferon antibodies has been reported in a patient being treated for leukemia.\textsuperscript{9}

Toyofuku et al\textsuperscript{23} described 6 observations of non-atopic patients with chronic HCV who developed erythematous papulovesicular, pruritic eruptions after interferon alfa therapy. Histopathologic studies showed epidermal spongiosis, papillary dermal edema, and perivascular dermal infiltrate of mononuclear cells. A nonallergic immunologic mechanism (cutaneous deposition of immune complexes) was proposed.

The mechanism for the severe nummular eczematous reaction to combination interferon alfa-2b plus ribavirin therapy in our patient with chronic HCV is unclear. The cutaneous effects of chronic HCV, such as pruritus and xerosis, may be exacerbated by interferon alfa-2b and/or ribavirin therapy. An underlying atopic predisposition may also play a role. However, a German study\textsuperscript{24} of interferon alfa-2a therapy in 12 patients with severe atopic dermatitis reported an aggravation in the condition in 1 patient and brief amelioration in 2 patients. Our patient had no history of atopy. The immunomodulatory effects of interferon alfa-2b are well known and may act locally and/or systemically. Ribavirin therapy may have a synergistic effect in predisposing to cutaneous reactions, as many of the reported cutaneous reactions to combination therapy have occurred in patients who had already received interferon mono-therapy.\textsuperscript{17,38} Our patient had received previous interferon therapy without cutaneous side effects.

It is likely that many more individuals treated with combination therapy for HCV have experienced or will develop similar cutaneous side effects. This eczematous reaction, though of a more moderate degree, seems to be relatively common in several European and South American centers, but North American dermatologists have not reported it. It is possible that smaller numbers of patients treated or referred from gastroenterologists may account for this. In presenting this report, we hope to make our colleagues aware of this unpleasant and potentially incapacitating sequel to HCV therapy.

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\textbf{Corresponding author and reprints:} David J. Elpers, MD, The Skin Clinic, 12 Meadow St, Williamstown, MA 01267 (e-mail: kauai@ecn.net).

\section*{References}


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