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.

Arch Dermatol. 2004;140:215-217
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. 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, interferon alfa-2b is still in use. Side effects are similar and common with both regimens, are often severe, and 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. A wide variety of injection-site reactions, including pyoderma gangrenosum, leukocytoclastic vasculitis, interface dermatitis, dermal hypersensitivity, necrotizing ulcerations, and suppurative and granulomatous dermatitis have been reported. Ribavirin has been associated with pruritus and photoallergic eczematous reactions. Several studies have shown an increase in cutaneous side effects in patients receiving combination therapy vs interferon monotherapy; 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 al 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-
zematos lesions, histopathologic studies were performed and showed superficial perivascular dermatitis with spon-
giosis. Unlike our patient, none of these patients modi-
ified their treatment because of their lesions, and all le-
sions resolved completely on termination of therapy.

Sookoian et al11 reported cutaneous reactions in 11
(33%) of 33 patients in Argentina with chronic HCV re-
ceiving interferon alfa (2a or 2b not specified) plus riba-
virin combination therapy vs 2 (6%) of 35 of those re-
ceiving interferon alone. Three of the patients in the com-
bination therapy group developed “eczema,” with his-
tologic diagnoses of “subacute psoriasiform dermati-
tis,” “eczema psoriasiform,” and “eczema.” The lesions
were limited to the arms and/or legs, unlike the gener-
alized presentation in our patient. Only 1 of the 11 pa-
tients with cutaneous adverse effects had to discontinue
treatment temporarily because of these effects.

Berger et al12 reported 4 cases of eczema in atopic pa-
tients in France with chronic HCV receiving interferon alfa-
2a or alfa-2b therapy. Three of these patients also took riba-
virin, and all had a history of certain or possible atopy. One
patient receiving combination therapy had nummular ec-
zema. Two of the patients receiving combination therapy
had received interferon monotherapy previously without ad-
verse dermatologic effects. In all these cases, the lesions be-
gan 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
delayed-type hypersensitivity with a positive patch test to interferon alfa-2c and an enzyme-linked immunosor-
bent assay positive for anti-interferon antibodies has been re-
ported in a patient being treated for leukemia.9

Toyofuku et al23 described 6 observations of non-
atopic patients with chronic HCV who developed ery-
thematos papulovesicular, pruritic eruptions after in-
terferon alfa therapy. Histopathologic studies showed epidermal spongiosis, papillary dermal edema, and peri-
vascular dermal infiltrate of mononuclear cells. A non-
allergic immunologic mechanism (cutaneous deposi-
tion of immune complexes) was proposed.

The mechanism for the severe nummular eczema re-
action 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 xe-
rosis, may be exacerbated by interferon alfa-2b and/or ri-
bavirin therapy. An underlying atopic predisposition may also play a role. However, a German study24 of interferon alfa-2a
therapy in 12 patients with severe atop cutaneous dermatitis re-
ported 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 predis-
posing to cutaneous reactions, as many of the reported cu-
taneous reactions to combination therapy have occurred in
patients who had already received interferon mono-
therapy.17,38 Our patient had received previous interferon ther-
yapy 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 re-
action, though of a more moderate degree, seems to be
relatively common in several European and South Amer-
ican centers, but North American dermatologists have not re-
ported it. It is possible that smaller numbers of pa-
tients treated or referral patterns from gastroenterolo-
gists may account for this. In presenting this report, we
hope to make our colleagues aware of this unpleasant
and potentially incapacitating sequela to HCV therapy.

Accepted for publication April 24, 2003.

We acknowledge the consent and cooperation of the patient described in this case.

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

REFERENCES

1. Manns MP, McHutchinson JG, Gordon SC, et al. International Hepatitis Inter-
ventional Therapy Group. Peginterferon alfa-2b plus ribavirin compared with in-
terferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a ran-

2. Poyiadji T, Marcellin P, Lee SS, et al. Randomised trial of interferon alfa-2b plus riba-
virin combination therapy vs 24 weeks versus interferon alfa-2b plus placebo for 48
weeks of treatment of chronic infection with hepatitis C virus. Lancet. 1998;
352:1426-1432.


5. Pawlotsky J-M, Dhumeaux D, Bapott M. Hepatitis C virus in dermatology: a re-

gangrenosum triggered by alpha 2b interferon in a patient with chronic granulo-

7. Christian MM, Diven DG, Sanchez RL, Sowolow RD. Injection site vasculitis in a
1997;37:118-120.

reaction induced by subcutaneous interleukin-2 and interferon alpha-2a immu-
notherapy following ABMT. Bone Marrow Transplant. 1993;11:443-446.

9. Detmar U, Agathos M, Nerl C. Allergy of delayed type to recombinant interferon
alfa 2c. Contact Dermatitis. 1989;20:149-150.


11. Matsukura M, Yamada H, Yamashita Y, Tazuka T. Local cutaneous necrosis fol-

P. Severe local cutaneous necrosis during treatment with interferon-alpha and riba-

13. Sanders S, Busan K, Tahan SR, Johnson RA, Sachs D. Granulomatous and sup-
purative dermatitis at interferon alfa injection sites: report of 2 cases. J Am Acad


15. Strzyjak-Kaminska D, Ochsenfort D, Roder C, Wolter M, Zeuzem S. Photodermat-


17. Davis GL. Current therapy for chronic hepatitis C. Gastroenterology. 2000;
118(2 suppl 1):S104-S114.

18. Maddrey WC. Safety of combination interferon alfa-2b/ribavirin therapy in chronic

19. McHutchinson JG, Gordon SC, Schiff EF, et al. Peginterferon alfa-2b alone or in com-
bination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med.

tions to interferon alfa-2b plus ribavirin therapy in patients with chronic hepa-

21. Sookoian S, Neglia V, Castano G, Frider B, Klein MC, Choeulea E. High preva-
ence of cutaneous reactions to interferon alfa plus ribavirin combination therapy

22. Berger L, Descamps V, March V, et al. Eczematous skin lesions induced by al-

23. Toyofuku K, Imayama S, Yasumoto S, Kiryu H, Mori Y. Clinical and immunohis-
tochemical studies of skin eruptions: relationships to administration of interferon-

24. Kropp JD, Algermissen B, Bock S. A pilot study on the effect of interferon alpha