

Injection Site Bullous Eruption and Generalized Rash Induced by Pegylated Interferon Treatment for Hepatitis C

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Cutaneous reactions to interferon in the treatment of chronic hepatitis C are not infrequent, as they are seen in up to 58% of patients. Usually, these reactions are self-limited and consist of erythema and induration at the injection site. More pronounced injection site reactions associated with generalized rashes away from the injection site are less common. We present the case of a patient who developed erythematous edematous vesiculobullous lesions at the injection sites, as well as a generalized rash.

Case Report

A 37-year-old woman of Korean ancestry with a medical history of gestational diabetes, rheumatoid arthritis, gastroesophageal reflux disease, and depression presented with fatigue and polyarthralgias. Her family history was notable for diabetes mellitus, and she did not have a prior history of atopy. The patient had no known drug allergies, and her current medications included venlafaxine (Effexor, Wyeth) and esomeprazole (Nexium, AstraZeneca). She was diagnosed with hepatitis C genotype 1B in March 2007, with a viral load of 9 million IU, and alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase levels of 52 U/L, 39 U/L, and 51 U/L, respectively. The patient's white blood cell count was 4,300/ μ , with a hemoglobin of 13.1 g/dL. A chronic liver disease evaluation was negative for alpha-1 antitrypsin deficiency, Wilson disease, hereditary hemochromatosis, autoimmune hepatitis, and primary biliary cirrhosis.

Synthetic liver function was preserved, with an albumin level of 4.4 g/dL, international normalized ratio of 1.0, and alpha fetoprotein level of 3.1 ng/mL. A right upper quadrant ultrasound showed a normal liver echotexture with a 1.4-cm right hepatic cyst.

A liver biopsy on April 2007 revealed grade 3 inflammatory changes and stage 2 fibrosis consistent with chronic active hepatitis. The patient was started on pegylated interferon alfa-2b (Pegintron Redipen, Schering) 80 mcg subcutaneously once weekly and ribavirin 400 mg twice daily. Seven days after the first injection into her left thigh, she developed an erythematous pruritic circular rash that was well circumscribed with blistering. The second injection into the right thigh resulted in a similar rash that developed more rapidly and was larger in size. She denied having any shortness of breath, wheezing, or fever.

By the time the patient was seen on October 5, 2007, she had administered 4 injections, 2 to each thigh. Pegylated interferon alfa-2b was discontinued, and she was referred for a dermatology consultation 3 days later. The dermatology consultant noted erythematous edematous vesiculobullous patches on the left thigh, with similar but less involvement on the right thigh. Her eyes and mouth were normal; however, there were discrete erythematous edematous papules on her forehead, arms, hands, back, and abdomen. These changes were suggestive of either contact dermatitis or erythema multiforme secondary to pegylated interferon alfa-2b. The patient was prescribed prednisone 40 mg daily with a 9-day taper and hydroxyzine 10 mg 1–3 tablets every 6 hours as needed for pruritus. She was advised to use Aveeno soaks to dry the bullous eruption.

At her 2-week follow-up, the patient had completed her course of prednisone, and bullae and pustules of the

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lower extremities had resolved, though she continued to have raised erythematous plaques with overlying scale. Pruritus and maculopapular rash on her bilateral upper extremities persisted. On November 5, 2007, her lower extremity rash had resolved and remained as a hyperpigmented patch. She underwent a punch biopsy of the persistent urticarial plaque on her right hand to rule out erythema multiforme. Pathology revealed superficial and deep angiocentric lymphocytic dermatitis with focal lichenoid-interface alteration suggestive of pernioitic reaction. These findings can be associated with connective tissue disease, paraproteinemia, Raynaud phenomenon, Crohn's disease, and hepatitis C infection; therefore, antinuclear antibody, serum protein electrophoresis, cryoglobulin, and cryofibrinogen measurements were obtained, revealing results within normal limits. The urticarial plaques ultimately improved with clobetasol ointment twice daily.

Despite a favorable response to interferon and ribavirin therapy, as evidenced by the patient's Week 4 viral load of 21,000 IU, it was decided to hold off treatment due to concern that the injection site rash could recur even with the use of a nonpegylated interferon preparation.

The pegylated interferon alfa-2b preparation does not have a preservative and is composed only of the active drug and sterile water. Therefore, this case likely describes a hypersensitivity reaction to the interferon itself. Whether the patient's history of rheumatoid arthritis and positive rheumatoid factor contributed to the severity of the reaction is unclear.

Discussion

In combination with ribavirin, pegylated interferon alfa-2b (as opposed to the nonpegylated formulation) is the preferred treatment for chronic hepatitis C. Pegylation of interferon improves the pharmacokinetics of the drug and results in prolonged antiviral activity and higher rates of sustained virologic response. Side effect profiles are similar between the two formulations; however, the frequency of their adverse effects can vary. According to one study comparing the efficacy of pegylated interferon alfa-2b to standard interferon-alfa both in combination with ribavirin, the overall frequency of adverse effects was 20% and the frequency of serious adverse effects was 1%.¹ The most common cutaneous reaction is localized injection site reaction or inflammation in up to 58% and 25% of patients, respectively. Only 36% of patients taking the standard dose of interferon complained of injection site reactions.¹ However, there are several reports of more pronounced injection site reactions associated with generalized exanthems from the use of interferon. This case represents a papulovesicular injection site reaction associ-

ated with a generalized rash that did not quickly resolve with the cessation of interferon therapy.

Generalized reactions that have been reported with the use of interferon include oral erosive lichen planus,² alopecia universalis,^{3,4} sarcoidosis,⁵ Meyerson naevi,⁶ and cutaneous polyarteritis nodosa.⁷ Localized reactions that have been reported include hyperpigmentation of the tongue,⁸ lupus-like injection site reaction,⁹ and facial erythema.¹⁰ Injection site ulceration has also been reported, though this was in a patient receiving interferon doses for the treatment of metastatic melanoma, which requires higher doses than hepatitis C treatment.¹¹

There have been several case reports of generalized cutaneous rashes while on interferon and ribavirin for the treatment of chronic hepatitis C. One such case involved a 46-year-old woman treated with pegylated interferon and ribavirin who developed pruritus and injection site papules as well as papules on her hands and feet.¹² She had a history of cutaneous reactions to other chemicals such as detergents. Ultimately, the lesions responded to antihistamines and did not recur after 4 weeks of therapy, and she was able to complete treatment. Another case involved a 50-year-old man who developed generalized nummular eczema 4 months after re-treatment with interferon alfa-2b 3 times weekly with ribavirin for relapse of previously treated hepatitis C virus. Therapy was discontinued, and he required prolonged prednisone treatment for symptom resolution.¹³ A case of injection site erythema and subsequent development of generalized erythematous macules and papules from interferon alfa-2a monotherapy has been reported.¹⁴ Hashimoto and associates reported a case of a 66-year-old woman initially treated with pegylated interferon-2b and ribavirin. She initially developed injection site reactions that subsequently became generalized vesicular and papular eruptions on her face, neck, trunk, and buttocks.¹⁵ She was treated with oral prednisolone, olopatadine, and topical diflucortolone. Her therapy was changed to interferon alfa-2a, but it was discontinued at the patient's request and the lesions did not recur. Skin biopsies remote from injection sites showed epidermal spongiosis, perivascular infiltration of the upper dermis of mostly CD4 lymphocytes, and no eosinophils, which is most consistent with an eczematous reaction. The researchers thought that this represented a modification or enhancement of the immune response, particularly as the injection site reaction persisted even after the interferon formulation was changed. They recommended that interferon treatment be combined with oral antihistamines and topical corticosteroids at the injection sites. If a generalized rash were to occur, the physician should consider prescribing low-dose prednisolone.

Cutaneous reactions from interferon have been found to be more pronounced with the addition of riba-

virin. Sookoian and colleagues studied 33 patients treated with 3 mU of interferon alfa-2b administered 3 times per week combined with 1,000–1,200 mg of ribavirin daily for 24 weeks.¹⁶ These patients were compared to 35 age-matched controls who received interferon alone for 6–12 months. Cutaneous reactions were significantly more frequent in the patients receiving combination therapy (33.4%) as opposed to the control patients (5.7%). The described reactions were mostly lichenoid-type reactions, but they also included eczema, nonspecific rash, and malar erythema. In the majority of treated patients, the cutaneous reactions completely resolved during the course of therapy. The recommendation was to closely observe patients on combination therapy.

Another study involved 210 patients from June 1998 to September 2000 who had no prior dermatologic history and were undergoing treatment for chronic hepatitis C virus with 3 mU of interferon 3 times per week and 1,200 mg ribavirin over 12 months.¹⁷ Only 27 patients in that group developed cutaneous lesions, the majority of which (59%) were eczematous and localized to the legs, arms, or trunk. However, 2 patients had generalized lesions. The average time of onset from the beginning of treatment was 3.2 months, with a range of 0.5–8 months. Pathology on 7 of these patients was notable for superficial perivascular dermatitis with spongiosis. Other noted lesions were prurigo, lichenoid eruption, seborrheic dermatitis, and maculopapular exanthem. All patients showed improvement with symptomatic treatment, which included antihistamines, moisturizing creams, and topical steroids. Once treatment with interferon and ribavirin was stopped, the lesions completely regressed. In this study, no patient had to discontinue therapy or undergo a dose readjustment.

A prospective study of 20 patients from the 90 patients referred to a center from 1999 to 2000 specifically examined the clinical and histologic pattern of inflammatory lesions outside the injection sites.¹⁸ These patients were comprised of 11 men and 9 women, with a mean age of 50 years. Two patients used the pegylated form of interferon, whereas the remainder used the nonpegylated formulation. Of that group, there was an equal use of either alfa-2a or alfa-2b, and the onset of lesions ranged from 2 weeks to 4 months. The clinical pattern was a pruritic, confluent, papular erythematous eruption mixed with vesicles most often located on the distal limbs, face, and neck. The lesions were infrequently seen on the trunk, axillae, and buttocks. Photosensitivity was also seen in 4 of the 20 patients. Histologic evaluation in 19 of the 20 patients revealed a nonspecific, often perivascular infiltrate in the upper dermis with a predominance of mononuclear cells occasionally accompanied by sparse keratinocyte necrosis with spongiosis and vesiculation.

Treatment was interrupted in half of the patients, resulting in clearing of the lesions in 2–3 weeks. The other half was able to complete therapy with the addition of antihistamines and corticosteroids. In 3 patients who were rechallenged with either the same or different formulation, 2 patients experienced recurrence of lesions. It should be noted that the patient in whom the formulation was changed experienced recurrence. The authors concluded that the incidence of cutaneous reactions distant to injection sites is likely to be low and that there are no clinical predictive factors. There was no trend toward a particular formulation of interferon being associated with cutaneous lesions.

The mechanism for the occurrence of cutaneous lesions due to interferon is not known. There has been speculation that immunomodulatory effects may be responsible for aberrant behavior of inappropriately stimulated T lymphocytes in response to normal stimuli such as light exposure, irritation, and slight trauma.¹⁸ A study examined the incidence of cutaneous reactions in 27 treatment-naïve patients and 10 previous nonresponders randomized to receive either pegylated interferon alfa-2b/ribavirin/amantadine or pegylated interferon alfa-2b and ribavirin.¹⁹ Nine patients developed cutaneous reactions, but 7 of those were in the triple therapy group. Biopsies in 6 of these patients showed focal spongiosis of the epidermis with occasional lymphocytic exocytosis. At the superficial dermis, there was edema and a perivascular lymphocytic infiltrate, but rare eosinophils. Treatment was withdrawn in 5 patients, 1 of whom had Darier disease prior to therapy. Recovery was slow, and 1 patient required oral prednisone. In the 4 cases in which therapy was continued, lesions subsided either with concomitant use of topical corticosteroids or with dose reduction of ribavirin.

The authors concluded that the high incidence of cutaneous reactions was likely due to synergic action of the drugs, particularly with the addition of amantadine. They also implicated pegylation as a contributing factor in the onset of cutaneous reactions, as it has been associated with contact dermatitis when used with some topical drugs and cosmetics. They noted that the skin lesions seen were more consistent with contact dermatitis as opposed to an allergic reaction due to the lack of eosinophils, and in 2 cases in which immunohistochemistry was performed, the presence of CD4-positive lymphocytes was noted. This suggested that the reactions were due to immune sensitization.

The mechanism for bullous lesions at the injection site is not understood as well. Montesu and colleagues reported a case of the development of bullous lesions at injection sites in a patient with chronic hepatitis C virus being treated with interferon alfa-2a and

ribavirin.²⁰ The lesions developed 3 months after the initiation of therapy, but there was no generalized rash. Biopsies revealed a subepidermic bulla with fibrinous content, edema, and lymphocytic and neutrophilic infiltrates in the papillar derma. Treatment was discontinued, and the lesions resolved with topical steroids. The authors concluded that since there were no vasculitic or necrotic components to the biopsy, the lesions may have been due to direct toxic action. A study of bullous lesions that developed in patients undergoing interferon treatment for Kaposi sarcoma suggested that there may be development of circulating immunoglobulin G antibodies to intercellular epidermal antigens similar to pemphigus. However, immunoprecipitation studies showed that the antigens were nonspecific and different from those seen in pemphigus.²¹

Summary

In the case presented here, the patient had no prior history of adverse skin reactions to any medication. She was treatment-naïve and initially developed a vesiculobullous injection site reaction to pegylated interferon alfa-2b and ribavirin within the first week of therapy that subsequently became a generalized rash. Due to the rapid onset and severity of symptoms, it was decided to stop therapy. Her lesions were slow to improve with topical and oral steroids. A rechallenge with nonpegylated interferon was not considered. Biopsy results were not consistent with a lichenoid or eczematous reaction, which is the most common type following treatment with pegylated interferon and ribavirin. It is possible that her generalized rash may have been a manifestation of her underlying disease. Cutaneous reactions of this type are not common, but it is important that physicians are aware of them. Early referral to a dermatologist and prompt symptomatic or even preventative treatment may be able to increase the likelihood of continuing antiviral therapy.

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Review

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Hepatitis C is a blood-borne infection of global epidemic concern. Its biggest risk factor is intravenous drug use, but it is also prevalent among healthcare workers and individuals with high-risk sexual behaviors. Chronic hepatitis C virus (HCV) infection is associated with significant morbidity and mortality; of the estimated 169.7 million people in the world infected with hepatitis C,¹ 3.2 million are in the United States, and it is the leading indication for liver transplantation.^{2,3} Pegylated interferon with ribavirin is the current standard of care for chronic hepatitis C treatment, but only 50–60% of patients will achieve sustained virologic response,⁴ with better outcomes associated with factors such as genotype 2/3 disease, race, advanced fibrosis, lack of co-infection with HIV, and a viral load of less than 600,000 IU/mL.⁵

Interferons exert their antiproliferative and antiviral activities by blocking HCV RNA translation and replication through protein kinase R and p56, along with the activation of innate immune systems through natural killer cells, B cells, and T cells.⁶ Standard interferon has a short half-life of 6–20 hours, but when covalently conjugated with polyethylene glycol, it has the advantage of improved pharmacokinetics with dosing changes to once-weekly dosing and greater therapeutic efficacy. The trade-offs include a reduction in biologic activity due to less robust binding to the interferon receptor and a change in side effect profile, in particular, greater hematologic abnormalities.^{7,8} Combination pegylated interferon and ribavirin also has a higher rate of injection site reactions compared to standard interferon and ribavirin.⁹ Cutaneous side effects of pegylated interferon are most common at the injection site and include necrotizing ulcerations¹⁰ and leukocytoclastic vasculitis,¹¹ though generalized skin rash (eg, exfoliative dermatitis, epidermal necrolysis, alopecia) is also noted.^{12,13}

Ribavirin exerts its antiviral activity by acting as an inosine 5'-monophosphatase inhibitor through its

metabolite ribavirin monophosphate. Although generally well tolerated, ribavirin's most common side effect is hemolytic anemia. Dermatologic adverse effects, including photoallergic reactions, occur in approximately 14% of patients.¹⁴ No clear underlying mechanism has been elucidated to explain the etiology of the cutaneous adverse reaction in patients receiving combination pegylated interferon and ribavirin; however, many different theories have been proposed, including cutaneous deposition of immune complex.¹⁵

The patient in the case report by Toney and Agrawal¹⁶ developed erythematous edematous vesiculobullous patches following subcutaneous injection of pegylated interferon alfa-2b (Pegintron Redipen, Schering) on both thighs and eventually developed generalized rash. Punch biopsy of the persistent urticarial plaque was suggestive of pernioic reactions. As the authors noted in their report, pernioic reaction is not specific and may be found in a variety of disease conditions, including viral hepatitis, cryoglobulinemia, and rheumatoid arthritis, or even as an abnormal reaction to cold or damp environments. The initial approach is to determine whether the above reaction was possibly caused by pegylated interferon alfa-2b. In this case, it is possible, and quite likely, that it was, in fact, due to the pegylated interferon alfa-2b and/or ribavirin. However, pegylated interferon alfa-2b, while containing no preservatives, contains additional additives, including dibasic sodium phosphate anhydrous, monobasic sodium phosphate hydrate, sucrose, and polysorbate 80, apart from its active ingredients. This is similar to peginterferon alfa-2a, which also contains additional additives, namely sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate trihydrate, and acetic acid. It is possible that the additives in the pegylated interferon alfa-2b preparation may have contributed toward the development of the cutaneous manifestations reported in this case, as some of the additives have been reported to cause hypersensitivity reactions with other preparations.

Steele and coworkers reported on two patients who developed hypersensitivity reactions while receiving darbepoetin and erythropoietin. Skin testing demonstrated that polysorbate 80 (Tween 80) used an excipient as the cause.¹⁵ Polysorbate 80 is a water-soluble polymer composed of fatty acid esters of polyoxyethylene sorbitan monooleate and is used as a solubilizing agent in biopharmaceuticals. It has also been shown to cause both respiratory and dermatologic side effects when used as an emulsifier in inhalation suspensions. Isaksson and colleagues reported a case of severe recurrent asthma in a patient with a negative prick test and no other signs of atopy. The patient was on budesonide-pressurized metered-dose inhaler as prophylaxis, along with different combinations

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of beta-2 agonists, and did not become symptom-free until budesonide was changed to a fluticasone propionate metered-dose inhaler, along with the same beta-2 agonist. The patient underwent skin patch testing for various types of allergens, including environmental and past exposed medications. The test was only positive for polysorbate 80, which was contained in the budesonide preparation.¹⁷ Grims and associates also showed that drug allergy could be due to “hidden” additives. One patient was falsely diagnosed with penicillin allergy. Due to inconsistent laboratory results, further skin testing was performed for both the additives and active ingredients, and the patient was later found to be sensitized to polysorbate 80, which was contained in the penicillin preparations.¹⁸

The case report by Toney and Agrawal¹⁶ adds to the list of possible cutaneous manifestations of peginterferon side effects and raises awareness of uncommon presentations of cutaneous manifestations of peginterferon and ribavirin. Although there is no standard algorithm with respect to adverse drug reaction, this patient may benefit from further diagnostic testings, including patch, prick, enzyme-linked immunosorbent assay, and, possibly, lymphocyte proliferation assay, not only to the active ingredients but also the additives associated with peginterferon alfa-2b. This may be particularly significant if repeat therapy is considered for this patient.

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