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Cutaneous Necrosis Associated with Recombinant Interferon Injection

Report of Three Cases with Interferon Beta–1b and Review of the Literature

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Interferons are cytokines produced by cells in response to stimulation by certain antigens and infectious agents. In recent years, recombinant interferons have been developed, which have antiviral, antiproliferative, and immunomodulatory functions. Several cutaneous reactions have been reported, including cutaneous ulceration at injection sites. We now report three cases of cutaneous ulceration caused by interferon β–1b injections. In addition, we review all of the previously reported cases of cutaneous ulceration caused by recombinant interferons and discuss the different mechanisms by which these substances may produce this effect. ***Key words: side-effect; treatment; multiple sclerosis.***

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Recombinant interferon beta (IFN β)–1b (Betaseron^r) was originally licensed in 1993 to reduce the frequency and severity of flares of multiple sclerosis (MS) (1, 2). The most commonly reported side-effects include local inflammatory injection site reactions, headache, fever, and a flu-like syndrome (1,3). In a trial of IFN β therapy for multiple sclerosis, 65% of the 226 patients had injection site reactions (2). Recently there have been several reports of cutaneous necrosis, secondary to IFN β–1b injections (4–6). We report three additional cases of local cutaneous necrotic ulcerations in patients on IFN β–1b for MS, review the other cases, and discuss the different potential mechanisms by which IFN treatment may produce cutaneous necrosis.

CASE REPORTS

Case 1

A 54-year-old black female with a history of MS and diabetes presented with an ulcerative lesion on the left abdomen, present for 1 month. She had used IFN β–1b injections, 9 million units subcutaneously (SQ) every other day (qOD), for 3 months. She also used subcutaneous injections of insulin for her diabetes, on her extremities, but only injected the IFN in the abdominal area.

Physical examination revealed a 1.7×0.8 cm ulceration on the left abdomen, at an IFN injection site. An eschar partially covered the surface, and there was hyperpigmentation and induration of the surrounding skin (Fig. 1).

Tissue cultures for fungi and acid fast bacilli were negative but grew *Staphylococcus aureus*. Biopsy revealed a superficial and deep mixed inflammatory infiltrate. Numerous ovoid spaces of variable size were present within the dermis, giving it a Swiss cheese appearance, similar to that seen in paraffinomas and silicone granulomas.

The patient was treated with mupirocin ointment (Bactroban®) and a hydrocolloid dressing (Duoderm®), and oral erythromycin for 10 days, with slow healing of the ulcer. The patient has continued to use the IFN β without further cutaneous reactions for 4 months.

Case 2

A 42-year-old white female with MS since 1986 was treated with IFN β–1b injections, 9.6 million units SQ qOD, beginning in May 1994. In July 1994, she developed a red macular lesion on her abdomen, which evolved into a 1.5×1.3 cm ulcer, with an overlying necrotic eschar. This healed without therapy in 4 months. Despite this, she continued to administer injections. She invariably developed a macular erythematous local reaction within 1 day of each additional injection, which resolved within several days.

In April 1995, however, she developed another ulcerative lesion at an injection site. This lesion measured 1.5×1.4 cm, with a necrotic base. This lesion also healed without therapy in several months, leaving hyperpigmented, atrophic scars. The patient continues to inject herself with IFN β–1b and has had no further ulcers. However, the self-limited erythema continues to develop following injection.

Case 3

A 52-year-old white female with a history of MS for 15 years had initially used IFN β–1b for 4 weeks, but her neurologist discontinued the medication when her disease flared. One month later she restarted the IFN β–1b at a dose of 9.6 million units SQ qOD. Ten weeks later, she developed multiple cutaneous lesions at the injection sites on her thighs bilaterally. These were initially erythematous patches, which subsequently became necrotic and ulcerated. When subsequently evaluated by the department of dermatology, she was noted to have multiple scars over the anterior thighs at prior injection sites (Fig. 2).

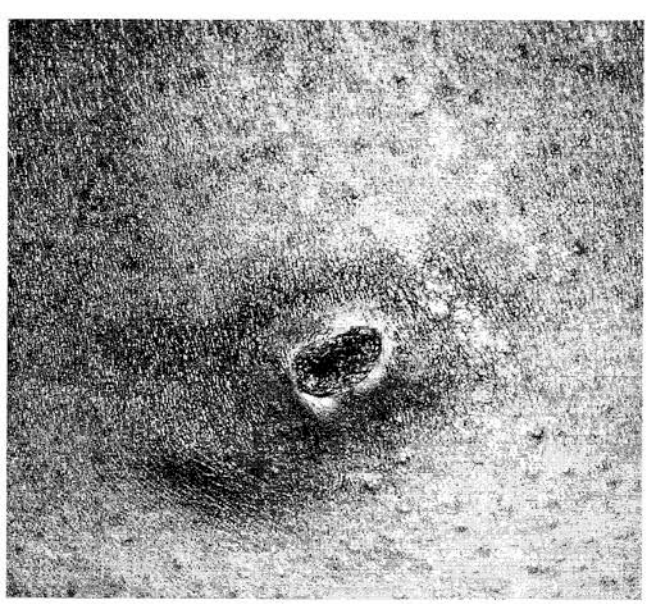

Fig. 1. Ulceration, with eschar partially covering the surface, at IFN β–1b injection site on the left abdomen, with hyperpigmentation and induration of the surrounding skin (Case 1).

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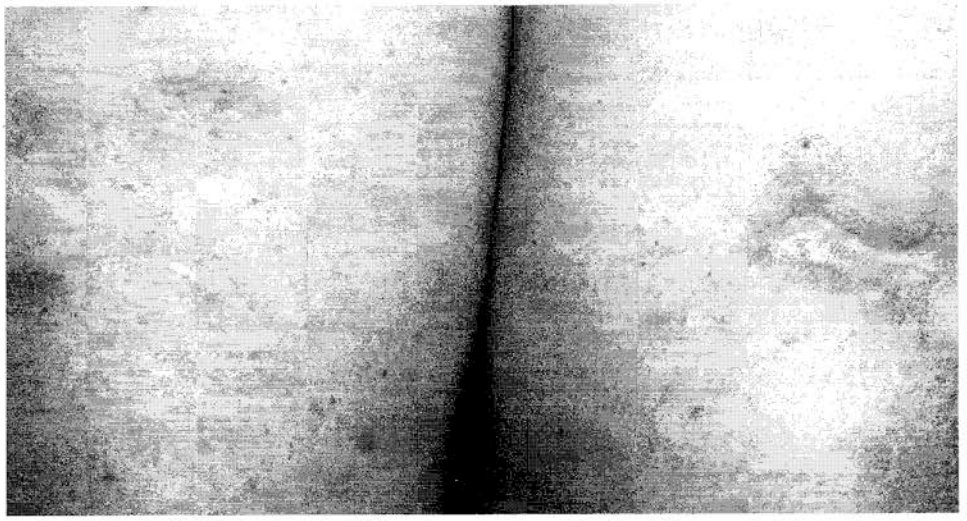

Fig. 2. Multiple scars over the anterior thighs at prior IFN β–1b injection sites, which had ulcerated (Case 3).

IFN was discontinued, and the patient was treated topically with vaseline gauze dressings, with resolution of her lesions. Wound cultures were negative, and no biopsy was obtained.

DISCUSSION

Local cutaneous reactions have been reported at injection sites of IFN therapy, but these are usually erythematous lesions which may rarely be indurated. More extensive local reactions have been reported over the last several years with different forms of interferon therapy. Cnudde et al. (7) first reported recombinant IFN–α-induced cutaneous necrosis at injection sites in a patient with AIDS-related Kaposi's sarcoma (KS). Two months after treatment, he developed localized erythema and then induration at the location of injection, which developed into dermal necrosis. Skin biopsy revealed thrombotic occlusion of venules. The patient had a history of congenital type II antithrombin (AT) III deficiency but normal protein C and S levels. The authors theorized that local necrosis resulted from a procoagulant activity of IFN, possibly provoked or potentiated by the AT III deficiency. Orlow & Friedman–Kien (8) have subsequently described a similar case of cutaneous ulcerations at sites of repeated injections of IFN α–2b (Intron A^r) in a patient with KS. In a similar case involving IFN α therapy (9), a patient with AIDS-related KS developed atrophic plaques on the lower abdomen at the sites of IFN injection. On histologic examination, these lesions showed necrotic changes within large venules deep in the dermis. A case of cutaneous necrosis has also been reported in a patient on IFN α therapy for chronic myelogenous leukemia (10).

With the advent of IFN β–1b therapy for MS, there have been reports of cutaneous necrosis associated with this therapy. Sheremata et al. (4) reported necrotizing cutaneous lesions complicating treatment in a 38-year-old woman with an 8-year history of MS, who developed erythema at injection sites on both thighs during the third month of treatment. These areas became violaceous, with a distinct livedoid pattern and black necrotic ulcerations, measuring 2 by 2 cm to 2 by 4 cm at their centers. Biopsy revealed focal thrombosis of vessels. The areas healed after IFN beta–1b had been discontinued.

In addition, Berard et al. (5) described a 56-year-old man with chronic hepatitis C infection, who developed cutaneous necrosis at injection sites in the abdominal area, after 6 months of treatment with IFN β. Biopsy revealed fibrin thrombosis of deep dermal vessels. There was no evidence of a coagulation abnormality in this patient. Most recently, Webster et al. (6) reported pain followed by ulceration at the injection site in 7 patients with MS receiving IFN β-1b. They hypothesized that production of endogenous mediators or coadministered medications may create situations promoting ulceration, or that there may be a vasospastic effect of the drug.

These cases of cutaneous ulceration in patients on IFN therapy suggest possible pathological mechanisms. Most of the cases with documented histologic findings suggest that thrombosis and necrosis of dermal vessels is an important aetiological factor (4,5,7,9). Such a local procoagulant effect may be caused by a toxic effect of the drug on the endothelium or a localized deficiency of an anticoagulant such as protein C (9). Orlow & Friedman–Kien attributed cutaneous ulceration to repeated injections in the same area. As in our first and second cases, this patient was able to continue injections in other skin sites without further complication (8).

In case 1, the histology suggests a foreign-body reaction to an exogenous material. The IFN β–1b contains no lipid substance, so that the nature of this reaction is unclear. The possibility of an accidental or iatrogenic introduction of an unrelated agent must be considered, although the patient reported that she was routinely careful in this process.

Further cases will provide more information on the pathogenesis of cutaneous necrosis secondary to IFN therapy. Biopsy data will be helpful in elucidating mechanisms, and may help to define subsets of cutaneous necrosis. In particular, it may be possible to define groups of patients in which IFN therapy may be continued at different injection sites, and those in whom the therapy must be discontinued. This latter group may include those who are predisposed to local thrombosis of dermal vessels as a result of an inherited or acquired coagulopathy, and who will therefore not be able to tolerate treatment.

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