Interferon-beta Induced Skin Necrosis

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Local cutaneous reactions have been reported at injection sites of interferon therapy, but these are usually erythema or rarely induration. Skin necrosis at the injection site is rare. We describe here a patient with multiple sclerosis who presented with cutaneous necrosis at the injection sites of interferon-β. Biopsy of the necrotic lesion showed dermal vessel thrombosis and complete ischemic coagulative necrosis of epidermis and dermis.


Key Words : Interferon, Skin necrosis, Multiple sclerosis, Thrombosis

Interferons, which have antiviral, antiproliferative, and immunomodulatory functions, are increasingly being used in the medical field. The most common side effects are flu-like symptoms. However, some cutaneous toxicities have been reported. These are usually erythematous lesions and indurations, but cutaneous necrosis is rare. We herein describe a 35-year-old female with multiple sclerosis (MS) who presented with multiple skin necrosis at the injection sites of recombinant interferon-β (rIFN-β).

CASE REPORT

A 35-year-old woman was diagnosed with multiple sclerosis in January 2002. The diagnosis of multiple sclerosis was established by recurrent episodes of visual loss and limb weakness over 3 years1. The patient began subcutaneously injecting rIFN-β1b (Beneserin) 9.6 million units every other day in July 2002. One month after treatment, she started to develop painful erythematous indurations at the injection sites. Most of these indurations resolved spontaneously but some evolved into necrotic ulcerating lesions, which healed after 3-4 weeks leaving atrophic scars.

In November 2002, skin examination revealed multiple ill-defined erythemas and inductions on the abdomen, thighs, and arms. In addition, there were 3 sharply demarcated, several millimeter, crusted ulcers with pinkish elevated edges on both thighs. Several whitish atrophic scars of similar sizes were also found (Fig. 1). Laboratory tests, including complete blood counts with differential counts, chemistry, electrolytes, lipid battery, prothrombin time, activated partial thromboplastin time, fibrinogen, protein C, protein S, Antithrombin III, lupus anticoagulant, anticardiolipin antibody, antinuclear antibody, anti-neutrophilic cytoplasmic antibody, and C-reactive protein were all within normal limits. Only erythrocytes sedimentation rate was increased to 31 (normal, <15mm/hr). Except rIFN-β, she was being treated with prednisolone, acetaminophen, and gabapentin.

The histologic finding of a necrotic ulcerating lesion showed a complete ischemic coagulative necrosis of epidermis and dermis (Fig. 2A). In mid-dermis, a few vessels of capillary or small venule size demonstrated thrombotic occlusion and necrosis (Fig. 2B). In other specimen, epidermal acanthosis, dermal hemorrhage and edema was noted adjacent to the necrotic area. Gram stain, periodic acid-Schiff stain, and Gomori-methenamine silver stain revealed no organisms. Tissue
Fig. 1. Multiple erythemas and indurations, 3 ulcers, and 1 atrophic scar (open arrow) are shown on the thighs at the injection sites of rIFN-β.

Fig. 2. A) Complete ischemic coagulative necrosis of epidermis and dermis. Pyknotic nuclear debris are found. Two thrombotic, necrotic vessels (arrows) are shown in the mid-dermis (H&E, ×40). B) A thrombosed dermal vessel (H&E, ×200).

Fig. 3. A sharply demarcated, irregularly shaped, deep ulcer with elevated border.

cultures for ordinary bacteria, fungi, and acid fast bacilli were negative too.

The patient was treated with mupirocin ointment, which slightly accelerated the healing. In spite of switching the drug to rIFN-β1a (Rebif®), new ulcerating lesions (Fig. 3) still continue to develop at every three to four injections.

**DISCUSSION**

rIFN-β was approved by the Food and Drug Ad-

ministration in 1993 for the treatment of multiple sclerosis. It has proved to be effective for decreasing the frequency and severity of flares of multiple sclerosis.

The most common side effects of interferons are flu-like symptoms, such as fever, headache, and myalgia. Several cutaneous reactions by rIFN-β include allergic contact dermatitis, psoriasis flare, and fatal pemphigus vulgaris. Local injection site reactions by rIFN-β are quite common; about 40-65% of MS patients develop cutaneous reactions at the injection sites, usually self-limiting erythematous lesions which may rarely be indurated. In 1995, Sheremata et al first reported necrotizing lesions complicating rIFN-β treatment in a female multiple sclerosis patient. Since then, there have been some reports of cutaneous necrosis associated
with rIFN-β therapy. About 1.5-5% of MS patients treated with rIFN-β developed ulceration or necrosis at the injection sites. According to Elgart et al., cutaneous reactions by rIFN-β varied from subtle uninflamed sclerotic dermal plaques to erythematous plaques to cutaneous ulcers. Ulcerations usually started as erythema and were replaced by gray discolorations that degenerated into ulcers. Some patients had livedo reticularis in the skin surrounding the injection site lesions. The firm sclerotic plaques showed fibrosis histologically, whereas nonsclerotic inflammatory lesions consistently showed vascular thrombosis. Other than necrosis, ulceration, and underlying thrombosis, the finding of superficial and deep perivascular, periadnexal, and interstitial mixed infiltration of lymphocytes, histiocytes, and neutrophils, mucin deposition was also recognized.

The mechanism by which rIFN-β induces ulceration is unknown. However, the consistent findings of dermal vessel thrombosis suggest localized procoagulant effect of interferon, direct cytotoxic damage to the endothelium, abnormality of platelet activation, or a coagulation disorder. Actually in some patients, coagulation abnormality was detected, such as antithrombin III deficiency and localized protein C deficiency. In addition, there is some evidence that multiple sclerosis patients have inherently enhanced platelet aggregation, which may be further enhanced by rIFN-β therapy.

In a case of diabetic patient reported by Weinberg et al., foreign body reaction to an axogenous material was also noted and S. aureus grew in the tissue culture. Fruland et al. reported a development of a well-differentiated squamous cell carcinoma in the ulcer which had been present for 6 months at the site of rIFN-β injection. These findings suggest that biopsy data can be crucial in defining subsets of cutaneous necrosis and providing a further treatment plan.

Except for appropriate local wound care, topical and oral antibiotics should be recommended to the secondly infected ulcers. In cases of inherited or acquired coagulopathy, rIFN-β therapy cannot be tolerated any more.

It is interesting that many patients begin to manifest the reaction after long periods of administration and many patients can continue the treatment, not being complicated by new ulcers. We hope that further accumulation in the experience of interferon therapy will elucidate the mechanisms of necrosis and guide to appropriate management.

REFERENCES