Skin Necrosis Following a Recombinant Interferon-beta-1b Injection

Chih-Hsun Yang, MD; Chien Hsun Chen, MD; Heng-Leong Chan[1], MD

Recombinant interferon beta-1b (INF-β-1b) has been proven to be an effective means of treating relapsing-remitting multiple sclerosis (MS). Adverse reactions to interferon therapy have been well documented. The most common side effects are transient influenza-like symptoms, including fever, fatigue, nausea, and myalgia. Cutaneous necrosis has occasionally been reported, mostly involving small and limited lesions. This article describes an MS patient who developed multiple large, deep cutaneous ulcers on INF-β-1b injection sites, which subsequently required surgical treatment. Vessel thrombosis in the subcutaneous fatty layer and the clinical appearance of livedoid erythema beside the ulcers indicated that INF-β-1b may have caused skin necrosis through its vascular effects. *(Chang Gung Med J 2002;25:774-7)*

Key words: interferon beta-1b, multiple sclerosis, skin necrosis.

Recombinant interferon beta-1b (INF-β-1b) is effective and was approved by the Food and Drug Administration (FDA) for the treatment of relapsing-remitting multiple sclerosis (MS) in 1993.[1] INF-β-1b, a synthetic analogue of recombinant human interferon beta produced in Escherichia coli, differs from native interferon beta in that it is non-glycosylated, lacks the N-terminal methionine, and has a serine residue substituted for cystine at position 17 to help stabilize the recombinant molecule.[2] Transient influenza-like symptoms are the most commonly mentioned side effects.[3] Cutaneous ulceration associated with INF-β-1b therapy has occasionally been described.[4-9]

CASE REPORT

A 40-year-old man with a 6-year history of MS had received subcutaneous injections of 8×10^6 units of recombinant INF-β-1b (Betaferon, Schering, Berlin, Germany) to all limbs and the abdomen on alternate days since July 1999. The patient tolerated the treatment well for the first 3 months, but painful reticulated erythematous patches later gradually developed at the injection sites, and eventually ulcerated after 2 to 3 weeks. However, the patient continued with the self-injections even after the skin broke down. Two months after the adverse cutaneous reactions, the man visited our outpatient clinic for evaluation of his skin ulcers. Examination revealed multiple ulcers surrounded by purpuric discoloration on his 4 limbs and abdomen. Four deep ulcers measuring 4×3 cm on the right thigh, 6×3 cm on the left thigh, 4×3 cm on the right upper arm, and 4×2 on the left upper arm were surrounded by a wide, irregular purpuric border (Fig. 1). These wounds were cleaned and conservatively treated with a hydrocolloid dressing (Duoderm®). By the next weekly visit, the wounds had enlarged and deepened, and the surrounding purpuric margin had also become ulcerated. Surgical excision was performed, and the defect on the right thigh was repaired using a rhomboid

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flap, while the other wounds were closed primarily. Skin histopathology revealed cutaneous necrosis down to the subcutaneous fat with vessel thrombosis (Fig. 2).

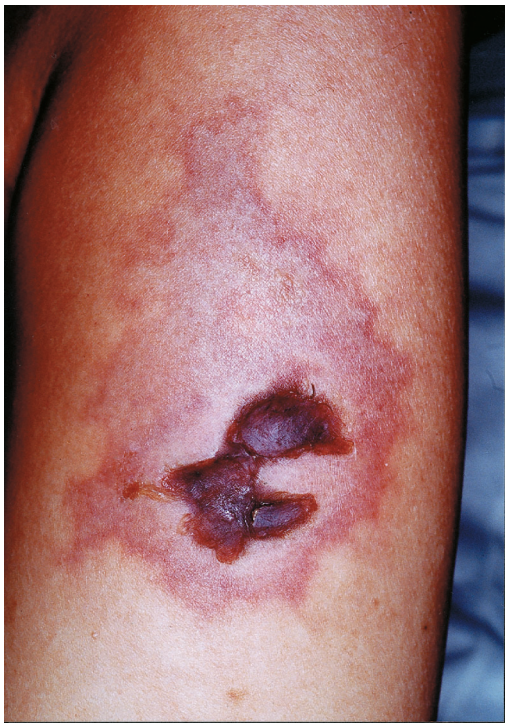

Fig. 1 A 4 ¡ 3-cm necrotic ulcer on the right upper arm covered with eschar at the INF-β-1b injection site and surrounded by wide, irregular erythema.

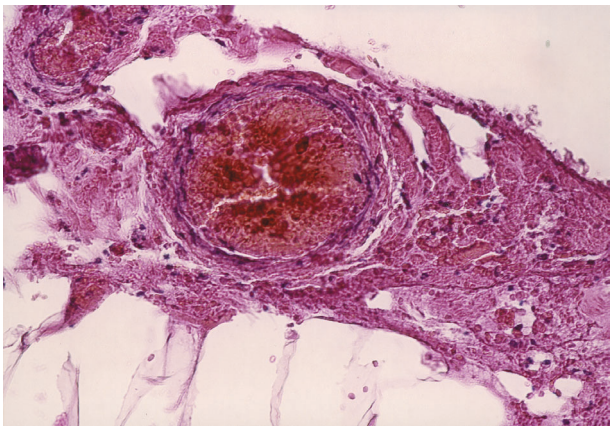

Fig. 2 A small arteriole thrombosis located in the deep subcutaneous fat. (H&E ¡ 100)

DISCUSSION

With the advent of recombinant DNA technology, human cytokines have become increasingly widespread in clinical applications. INF-β-1b has been proven effective in reducing the frequency and severity of MS. The therapeutic mechanisms of INF-β-1b remain unknown, but it probably acts through an antiviral or immunomodulation pathway by increasing natural killer cells and reducing interferon gamma production.[1]

Adverse reactions to interferon therapy have been well documented, and include transient influenza-like symptoms as well as dizziness, vomiting, arthralgia, and depression.[3] Skin necrosis after interferon therapy was first reported in a patient with acquired immunodeficiency syndrome at interferon-alpha-2b injection sites.[10] The authors suggested that the skin ulceration was related to local interferon procoagulant activity, since the patient suffered from congenital antithrombin III deficiency, and a biopsy specimen revealed thrombotic occlusion of the small dermal venules. Sheremata et al.[4] first described erythematous patches followed by necrotic ulcers with violaceous livedoid borders around INF-β-1b injection sites 3 months after the start of the injections in an MS patient. Perivascular and interstitial lymphocyte infiltration with focal thrombosis of vessels was noted. In a multicenter controlled study of INF-β-1b therapy, 69% of the 372 MS patients who received 8 ¡ 10^6 IU (MIU) of INF-β-1b every other day had inflammatory reactions at the injection site, compared to 6% of all patients who received placebo injections.[3] Another study described cutaneous ulcers developing and pustular psoriasis flaring up in 8 of 400 MS patients an average of 13 weeks after beginning INF-β-1b therapy.[5]

The mechanism by which INF-β-1b induces ulceration is unknown. The onset of pain soon after injection and the distinct livedoid pattern surrounding the full-thickness necrotic skin imply that the drug has a local vasospastic effect.[5] Meanwhile, perivascular and interstitial lymphocytic and histiocytic cell infiltrations and vessel thrombosis indicate a vascular or immunological-related process.[4-7] However, a local reaction to improperly dissolved lyophilized substances may have been involved because modifying the mixing procedures and injecting the drug at body temperature prevented further

necrosis.[8]

In a review of the literature, most patients who developed cutaneous ulceration withdrew from INF-β-1b therapy following the onset of skin breakdown, and only considered that the reaction was possibly transitory and eventually became tolerable.[5,9] The small, shallow ulcers may gradually resolve under proper wound dressing.[6] However, treatments such as antibiotics and high-dose intravenous steroids were ineffective in preventing tenderness or halting progression of the ulceration.[7] The patient in this investigation was intolerant of repeated INF-β-1b injections. Owing to the insidious nature of the reactions and the fact that the ulcerations did not fully manifest themselves until several weeks after the injection, the patient was unaware of the condition and presented to us with several large ulcers 2 months after the onset of the cutaneous reaction. Consequently, we surgically excised them to save the time and costs of bandaging and daily care, since large ulcers such as these may have taken up to several months to heal, and scarring would have been inevitable.[9]

To prevent adverse cutaneous side effects, patients who self-inject INF-β-1b should be advised to contact doctors on the appearance of redness, swelling, discoloration, pain, or inflammation of the skin around the injection site, since ulceration will not appear until several weeks after the injections. Patients with inherited or acquired coagulopathy are not suitable for INF-β-1b therapy. As some patients have experienced healing of their skin ulcers and become tolerant to further injections, patients with single and shallow ulcers may continue on INF-β-1b under close supervision. Meanwhile, for patients with multiple lesions and deep ulcers, INF-β-1b should be discontinued until healing is complete. Injecting INF-β-1b using proper aseptic techniques and rotating injection sites with each dose will help minimize the risk of injection site necrosis. Finally, surgical interventions were cosmetically helpful and reduced wound management time.

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干擾素β-1b皮下注射引起的皮膚潰瘍

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皮下注射干擾素β-1b已經證實可以有效緩解反復發作型的多發性硬化症病患。此藥物治療的原理尚未明瞭，但有可能是經由抗病毒或免疫調節的機轉。 干擾素β-1b注射最常見的副作用包括了發燒，疲倦，肌肉酸痛，嘔心等類似感冒的症狀。皮膚潰瘍的不良反應在過去報告中並不常見，而且大多數是單一的小型潰瘍。我們報告一例患有多發性硬化症的病患在接受了干擾素β-1b皮下注射後，在四肢注射處產生多處大範圍的皮膚潰瘍。這些皮膚潰瘍最後採用手術切除及縫合。由於在病理切片下可以發現位於皮下脂肪層的血管阻塞，以及臨床上在皮膚潰瘍週圍呈現廣泛紅斑，我們推斷干擾素β-1b注射後引起局部的血管病變造可能是造成皮膚潰瘍的原因。(長庚醫誌 2002;25:774-7)

關鍵字：干擾素β-1b，多發性硬化症，皮膚潰瘍。

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