Severe Necrosis and Cellulitis Complicating Treatment with Interferon β-1a

Chun-Chen Chang¹, Chien-Hui Lin², Jen-Jen Su³

Abstract

Purpose: A case report with a review of the current literature concerning cutaneous necrosis has occasionally been reported in interferon therapy.

Case report: We report a 19-year-old woman diagnosed multiple sclerosis for three years. She self-injected the standard dose of recombinant interferonβ-1a (12 million units) subcutaneously three times a week. Severe necrotizing cutaneous reactions over abdomen Happened and she must receive parental antibiotics and surgical debridement.

Conclusion: Our observation emphasizes the importance of educating patients on the proper self-administration of subcutaneous injections of interferon β.

Keywords: Multiple sclerosis (MS), Interferon (IFN) β-1a, Skin necrosis, Neuromyelitis optica (NMO)

Severe Necrosis and Cellulitis Complicating Treatment with Interferon β-1a

INTRODUCTION

Recombinant Interferon (IFN) -β has been used to modify the course and to reduce relapse in patients with relapsing-remitting MS (RRMS). All of IFNs for the treatment of MS requires indefinite injection therapy, which has been associated with a variety of adverse effects of skin including pain, infection and occasional necrosis. Subcutaneous injection of IFN can result in a greater number of local adverse events compared with intramuscular therapy. Rebif is a form of INF-β known as INF-β-1a, identical to the naturally occurring protein found in the human body. Here, we report a young female initially diagnosed RRMS, who after receiving self-injected Rebif, experienced abdominal cutaneous cellulitis and necrosis requiring surgical debridement.

CASE REPORT

A 28 year-old woman was diagnosed with RRMS when she was 16 years old and routinely received subcutaneous injections of Rebif.

Progressive erythema and tenderness in the lower left abdominal wall followed by the development of erythematous papules, becoming necrotic in areas, happened to her when she was 19 years old. Pus was discovered in the left lower quadrant (LLQ) of the necrosis site approximately whereupon the patient visited a local...
However, antipyretics were unable to relieve the accompanying fever, the patient went to our emergency room (ER) for help. The patient was conscious and communicating clearly. The patient’s blood pressure was 109/57 mmHg, with a heart rate of 52 beats per minute and respiratory rate of 18 breaths per minute. During the physical examination, the patient’s abdomen was soft and flat. Except LLQ, no tenderness, rebound pain, or Murphy’s sign were detected. Normoactive bowel sounds were audible. Two necrotic wounds were noted in the right lower quadrant and the LLQ, with local erythema, swelling, heat, pain, and pus noted associated with the wound in the LLQ (Fig. 1-A, B, C). Mild paresis of the left leg and hand (4/5 on MRC scale), exaggerated tendon reflexes of both ankles were detected. Pinpricks decreased from the 4th thoracic dermatome. No leukocytosis (white blood cell: 8500/ul) but a shift to left (Seg: 83 %; reference 40-75%) was noted. Subcutaneous cellulitis at the site of the injection was suspected. The wound was cleaned and dressed, and the patient was administered Oxacillin. Local erythema, swelling, heat, and pain were relieved; however, intermittent fever of up to 39 °C with chills and a sudden onset of bilateral lower limb weakness with back pain was noted two days following admission. Thoracic magnetic resonance imaging showed multiple T2 hyperintense intramedullary patchy lesions between the 4th and 12th thoracic level. (Figure. 2) Due to long segmental spinal cord lesion and abnormal visual evoked potential neuromyelitis optica (NMO) but not MS was suspected confirmed by positive anti-aquaporin antibody.

The patient was treated with intravenous high-dose solumedrol (1g/day) for three consecutive days followed by oral predonin. Parenteral Cefmetazole was changed for the presence of Serratia marcescens shown in pus cultures.

Figure 1. Two necrotic skin ulcers on the right and left lower quadrant of abdomen were shown separately, with surrounding erythema. A subcutaneous pocket with pus accumulation in the necrotic ulcer over left lower quadrant of abdomen. (1-A). wound at initial admission. (1-B). wound before debridement. (1-C). wound after debridement. (1-D). Computed tomography of the abdomen without intravenous contrast enhancement shows focal subcutaneous swelling and fatty infiltration with small gas formation at left lower quadrant of abdomen (about 2.5cm). The underlying abdominal muscle is intact. Cellulitis with localized abscess at left lower abdominal wall is considered.
No fever occurred and local swelling, erythema, and pain abated. Abdominal computed tomography showed an unclosed wound of 2.5 cm in the LLQ with intact underlying abdominal muscle. (Fig. 1-D). The patient underwent surgery for debridement, revealing a 5*5 cm subcutaneous pocket with necrotic tissue and accumulated pus. The patient had rehabilitation and discharged after wound sutured.

**DISCUSSION**

IFN-β is known to act on multiple pathways and inhibit the proliferation of leukocytes and antigen presentation, cytokine production, and T-cell migration across the blood–brain barrier (1). Adverse reactions to IFN therapy have been well documented, including transient influenza-like symptoms as well as dizziness, vomiting, arthralgia, transient laboratory abnormalities, mental disorders, and depression (1). Dermatological complications of subcutaneous injections of IFN including erythematous plaques, sclerotic dermal plaques, sarcoid like granulomatous dermatitis, and ulcers are also not uncommon (2).

Several INFs have been introduced for the treatment of MS, including IFNβ-1b (Betaseron) and two IFNβ-1a preparation (Avonex and Rebif) (3). Rebif, given subcutaneously, can cause significant skin reactions including skin necrosis at injection sites, a problem that has not been observed with Avonex which was given intramuscularly (3).

Skin necrosis following IFN therapy was first reported in a patient with acquired immunodeficiency syndrome at IFN-alpha-2b injection sites (4). Sheremata et al. first described cutaneous necrosis in an MS patient, surrounding the injection sites of INF-β-1b three months after the initiation of treatment (5).

The mechanism behind IFN-induced cutaneous necrosis is unclear, although a direct toxic effect on the vascular endothelium has been postulated (6). Identifiable risk factors include incorrect injection techniques, inappropriate needle length, and repeated use of the same injection site (2). Due to a high proportion of subcutaneous fat, skin reactions have been reported less frequently in the abdomen and buttocks, compared with the arms and thighs (2).

The patient in this case felt less pain when IFN was injected on the abdomen, possibly due to hypoesthesia following a previous attack of thoracic myelitis, which may explain why she did not seek medical attention until a subcutaneous pocket with pus had formed. Discontinuation of IFN therapy following the development of cutaneous necrosis has been advocated (6). Surgical interventions are cosmetically helpful and reduce wound management time. Recent case reports and series have shown that patients with NMO experience clinical deterioration under IFN-β treatment. In patients with NMO, IFN-β treatment is not only ineffective for preventing relapses but also may even increase relapses significantly (7). Because of previous attacks of optic neuritis and myelitis, the initial diagnosis of MS was suspected then shifted to NMO after positive anti-aquaporin antibody shown. To our patient, no IFN-β was re-titrated and she received surgical debridement. We kept the patient on a low dose of steroids with added azathioprine.

To prevent adverse cutaneous side effects, patients who self-inject IFN-β should be advised to contact doctors upon the first appearance of redness, swelling, discoloration, pain, or inflammation of the skin.
## Table. Case reports for patient with cutaneous adverse effect after subcutaneous DMT injection.

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Sex</th>
<th>Age</th>
<th>Cutaneous lesion</th>
<th>DMT</th>
<th>Duration of Rx</th>
<th>Biopsy/Pathology</th>
<th>Management</th>
<th>Prognosis</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>US</td>
<td>F</td>
<td>38</td>
<td>erythematous patches</td>
<td>INF-β-1b</td>
<td>3 months</td>
<td>marked acanthosis superficial and deep perivascular and interstitial lymphocytic and histiocytic infiltrates mixed with neutrophils</td>
<td>Interferon withdrawal wound care</td>
<td>interferon alfa-n3</td>
<td>5</td>
</tr>
<tr>
<td>1997</td>
<td>Italy</td>
<td>M</td>
<td>38</td>
<td>multiple severe necrotic skin ulcers</td>
<td>INF-β-1b</td>
<td>3 months</td>
<td>not recorded</td>
<td>unknown</td>
<td>modify the mixing procedure</td>
<td>8</td>
</tr>
<tr>
<td>1997</td>
<td>US</td>
<td>F</td>
<td>54</td>
<td>ulcer</td>
<td>INF-β-1b</td>
<td>3 months</td>
<td>not recorded</td>
<td>unknown</td>
<td>modify the mixing procedure</td>
<td>8</td>
</tr>
<tr>
<td>2002</td>
<td>Taiwan</td>
<td>M</td>
<td>40</td>
<td>painful reticulated erythematous patches</td>
<td>INF-β-1b</td>
<td>3 months</td>
<td>cutaneous necrosis down to the subcutaneous fat with vessel thrombosis</td>
<td>surgical excision</td>
<td>unknown</td>
<td>10</td>
</tr>
<tr>
<td>2003</td>
<td>Italy</td>
<td>F</td>
<td>43</td>
<td>ulcers after 2-3 weeks</td>
<td>INF-β-1b</td>
<td>2 months</td>
<td>confluent necrosis of the superficial and deep skin tissue with mild infiltration by inflammatory cells and thrombosis in deep blood vessels</td>
<td>re-introduce</td>
<td>interferon withdrawal corticosteroid</td>
<td>11</td>
</tr>
<tr>
<td>2006</td>
<td>Spain</td>
<td>F</td>
<td>38</td>
<td>persistent cutaneous rash and vascular dermatitis</td>
<td>INF-β-1b</td>
<td>16 months</td>
<td>ischemic necrosis of dermis and epidermis, with a lymphoplasmacytic infiltrate and blood extravasation in the reticular dermis among numerous thrombosed arterial vessels</td>
<td>GA withdrawal</td>
<td>azathioprine lesions healed over 2-3 weeks once treatment was interrupted.</td>
<td>12</td>
</tr>
<tr>
<td>2007</td>
<td>French</td>
<td>F</td>
<td>22</td>
<td>extremely painful induration</td>
<td>INF-β-1a</td>
<td>several months</td>
<td>ischemic necrosis of dermis and epidermis, with a lymphoplasmacytic infiltrate and blood extravasation in the reticular dermis among numerous thrombosed arterial vessels</td>
<td>surgical debridement</td>
<td>interferon withdrawal</td>
<td>13</td>
</tr>
<tr>
<td>2013</td>
<td>Italy</td>
<td>M</td>
<td>52</td>
<td>patient also had psoriasis</td>
<td>INF-β-1b</td>
<td>10 years</td>
<td>ischemic necrosis of dermis and epidermis, with a lymphoplasmacytic infiltrate and blood extravasation in the reticular dermis among numerous thrombosed arterial vessels</td>
<td>surgical debridement</td>
<td>interferon withdrawal</td>
<td>16</td>
</tr>
</tbody>
</table>

**DMT:** disease modify therapy  
**INF:** interferon  
**GA:** glacier acetate

---

*Acta Neurologica Taiwanica Vol 29 No 3 September 2020*
surrounding the injection site. Injection of IFN-β using proper aseptic techniques and rotating injection sites with each dose minimizes the risk of necrosis at the injection site.\(^6\)

In conclusion, cellulitis and abscess are a rare and severe complication of IFN-β. Careful skin examination at injection sites is recommended for all patients, particularly those with myelopathy, to prevent potentially severe local skin infections.

Conflicts of interest:
We have no conflicts of interest.

IRB:
The study had been approved by National Taiwan University Hospital
IRB (No. 201806036RIND)

Acknowledgments:
We thank the plastic surgeon at National Taiwan University Hospital for debridement and suture for the patient.

REFERENCE