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

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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)

Acta Neurol Taiwan 2020;29:90-94

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

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Received December 11, 2018. Revised February 20, 2019. Accepted May 15, 2020.
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clinic. 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.

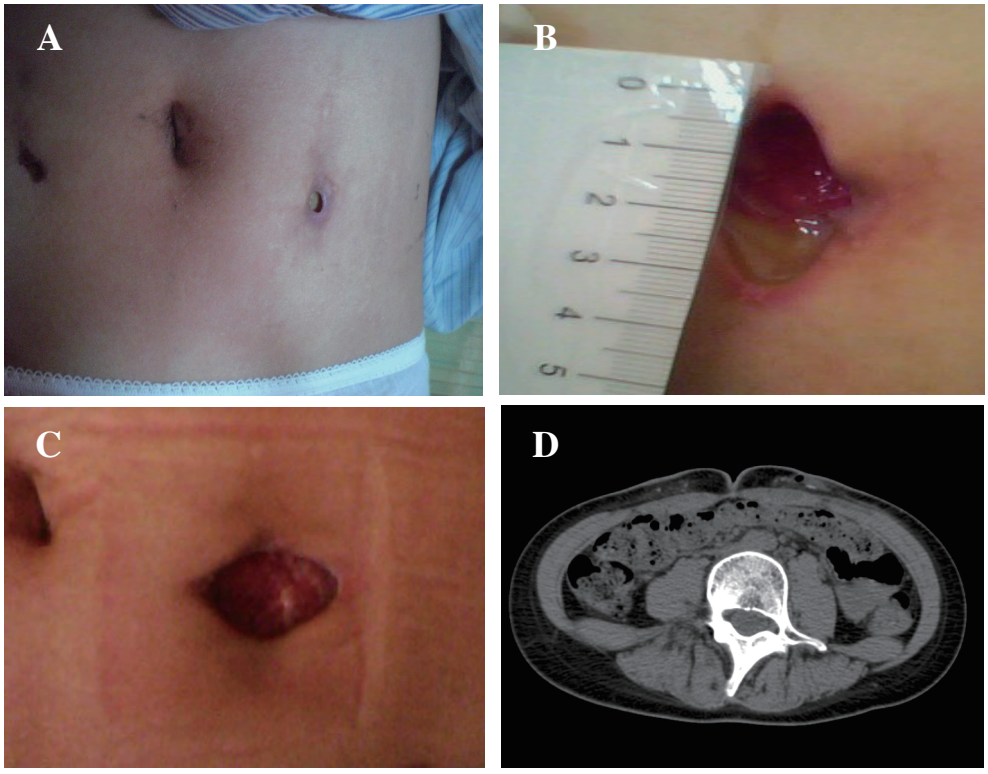

Figure 1. Two necrotic skin ulcers on the right and left lower quadrant of abdomen were shown separately, with surrounding erythema. A subcutaneous pocket with pus accumulation in the necrotic ulcer over left lower quadrant of abdomen. (1-A). wound at initial admission. (1-B). wound before debridement. (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.

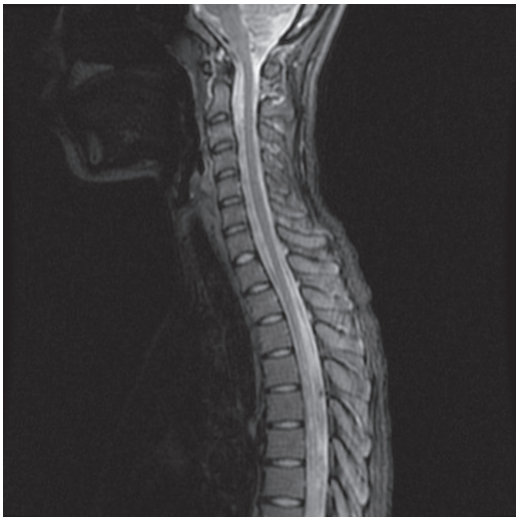

Figure 2. MRI of whole spine without contrast enhancement shows multiple T2 hyperintense intramedullary patchy lesions at the T4-T12 level. There was atrophic change of the thoracic spinal cord. The extension of the lesion is slightly longer as compared with the prior image done two years ago.

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, give 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-ß treatment. In patients with NMO, IFN-ß 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.

Year	Country	Sex	Age	Cutaneous lesion	DMT	Duration of Rx	Biopsy/Pathology	Management	Prognosis	Ref
1995	US	F	38	erythematous patches	INF-β-1b	3 months	marked acanthosis superficial and deep perivascular and interstitial lymphocytic and histiocytic infiltrates mixed with neutrophils	Interferon withdrawal wound care	interferon alfa-n3	5
1997	Italy	M	38	multiple severe necrotic skin ulcers	INF-β-1b	3 months	not recorded	unknown	modify the mixing procedure	8
1997	US	F	54	ulcer	INF-β-1b	3 months	superficial and deep mixed inflammatory infiltration with Swiss cheese appearance	wound care	further INF-β-1b usage long-term healing process	9
		F	46	necrotic skin ulcer	INF-β-1b	2 months	not performed	healed without therapy	keep INF-β-1b usage	
		F	52	erythematous patch then necrotic ulcer	INF-β-1b	2 weeks	not performed	Interferon withdrawal wound care	unknown	
2002	Taiwan	M	40	painful reticulated erythematous patches ulcers after 2-3 weeks	INF-β-1b	3 months	cutaneous necrosis down to the subcutaneous fat with vessel thrombosis	surgical excision repair by flap	unknown	10
2003	Italy	F	43	ulcers	INF-β-1b	2 months	confluent necrosis of the superficial and deep skin tissue with mild infiltration by inflammatory cells and thrombosis in deep blood vessels	Interferon withdrawal corticosteroid	the skin vasculopathy lesions healed after 12 months	11
2006	Spain	F	38	persistent cutaneous rash and vascular dermatitis	IFN	not recorded				12
				erythematous plaques ulcer after ten days	GA	16 months	ischemic necrosis of dermis and epidermis, with a lymphoplasmacytic infiltrate and blood extravasation in the reticular dermis among numerous thrombosed arterial vessel	GA withdrawal	azathioprine lesions healed over 2–3 weeks once treatment was interrupted.	
		M	27	erythematous painless plaque ulcer after one week	GA	18 months	ischemic necrosis of dermis and epidermis	GA withdrawal	IFN-β-1a lesion healed over weeks	
2007	French	F	22	extremely painful induration	IFN-β-1a	several months	vasculitis and capillary thrombosis	surgical debridement Interferon withdrawal	re-introduce	13
		F	45	extremely painful induration		several months	dermal edema	plasty for debridement Interferon withdrawal	re-introduce	
2013	Italy	M	52	patient also had psoriasis injection-site cutaneous necrosis radial nerve palsy	GA	21 months	cutaneous necrosis involves both subcutaneous and muscular tissue with massive edema	oral predonin vacuum-assisted closure physical therapy	dimethyl fumarate radial nerve palsy persisted	14
2015	Iran	F	49	erythematous patches and plaques progressed to necrotic ulcer	IFN-β-1b	3 months	nonspecific inflammatory reactions No evidence of vasculitis and granulomatous reactions	GA withdrawal surgical debridement skin grafting Interferon withdrawal	IFN-β-1a intramuscular	15
2020	Iran	F	55	skin and subcutaneous tissue necrosis	IFN-β-1b	10 years	nonspecific inflammatory reactions with no evidence of vasculitis or granulomatous reactions	surgical debridement Interferon withdrawal	IFN-β-1a intramuscular	16
1995	US	F	38	marked acanthosis superficial and deep perivascular and interstitial lymphocytic and histiocytic infiltrates mixed with neutrophils	INF-β-1b				interferon alfa-n3	
1997	Italy	M	38	multiple severe necrotic skin ulcers with surrounding erythema	INF-β-1b	3 months			modify the mixing procedure	1997
2002	Taiwan	M	40	painful reticulated erythematous patches	INF-β-1b	3 months	cutaneous necrosis down to the subcutaneous	Surgical excision		
				eventually ulcerated after 2 to 3 weeks	Betaferon		fat with vessel thrombosis	repair by flap		
2006	Spain	F	38	persistent cutaneous rash and vascular dermatitis	Interferon					
				several abdominal erythematous plaques which turned to blisters over a lilaceous base surrounded by livedo reticularis, and finally became ulcerated in ten days	Copaxone	16 months	ischemic necrosis of dermis and epidermis		azathioprine healed after 2-3 weeks	
		M	27	erythematous painless plaque became violaceous and ulcerous in one week	Copaxone	19 months	ischemic necrosis of dermis and epidermis		interferon -1 a healed slowly	
2007	French	F	22	extremely painful induration	IFN-β-1a	several months	vasculitis and capillary thrombosis	plasty for debridement Interferon withdrawal	re-introduce	
		F	45	extremely painful induration		several months	dermal edema	plasty for debridement Interferon withdrawal	re-introduce	
2013	Italy	M	52	injection-site cutaneous necrosis severe edema radial nerve palsy	Copaxone	21 months		oral predonin vacuum-assisted closure physical therapy	dimethyl fumarate radial nerve palsy persisted	
2015	Iran	F	49	erythematous patches and plaques progressed to areas of indurated erythema with central necrotic ulceration	IFN-β-1b	3 months	nonspecific inflammatory reactions No evidence of vasculitis and granulomatous reactions	plasty for debridement	interferon-1b intramuscularly	

DMT: disease modify therapy IFN: interferon GA: glacier acetate

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.

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