Journal of Research in Pharmacy Practice

Case Report

Multiple cutaneous necrotic lesions associated with Interferon beta-1b injection for multiple sclerosis treatment: A case report and literature review

Gita Faghihi[1], Akram Basiri[1], Mohsen Pourazizi[2], Bahareh Abtahi-Naeini[3], Ali Saffaei[4]

[1]Department of Dermatology, Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[2]Students' Research Committee, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran

[3]Department of Dermatology, Skin Diseases and Leishmaniasis Research Center, Students' Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran

[4]Pharmacy Students' Research Committee, School of Pharmacy, Isfahan University of Medical sciences, Isfahan, Iran

Received: January 2015
Accepted: March 2015

Corresponding author:
Dr. Bahareh Abtahi-Naeini,
E-mail: Bahareh.abtahi@yahoo.com

ABSTRACT

Multiple sclerosis (MS) is a chronic and debilitating inflammatory autoimmune disorder of the central nervous system. MS patients may experience severe local inflammatory skin reactions during disease-modifying therapy with subcutaneously injected interferon-beta-1b (IFN-β). We report the case of a 49-year-old woman with relapsing-remitting MS, who developed multiple cutaneous necrotic ulcers on both arms and thighs after 3 months of treatment with subcutaneous IFN-β-1b. The biopsy specimens showed skin and subcutaneous tissue necrosis. We diagnosed the skin lesions as cutaneous necrotic ulcerations associated with IFN-β-1b injection. The treatment included ending the use of subcutaneously injected IFN-β-1b and switching to intramuscularly injected IFN-β-1a because of the multiple cutaneous necrotic ulcers. The injection of IFN-β-1b in the areas with lesions was stopped, and the patient's clinical condition improved with the addition of routine wound care, surgical debridement, and skin grafting. This report is intended to raise awareness about severe adverse skin reactions which may rarely occur with subcutaneous IFN-β-1b injection. Early recognition and correction of the injection technique and switching to other forms of interferon can help to prevent these complications.

Keywords: Interferon beta-1b; multiple sclerosis; necrotic cutaneous ulcer

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disorder of the central nervous system.[1] The principal therapeutic option available for this disease consists of immunomodulators like interferon-beta (IFN-β), which reduce the frequency of exacerbations and control the activity and progression of MS.[2] The use of this drug is followed by certain usual side effects, like secondary dermatological manifestations, which are normally seen as skin reactions where there has been subcutaneous application.[2,3]

Cutaneous reactions at injection sites are frequently observed (in 44% of patients), ranging from benign painful erythema to skin necrosis.[4] With the increasing use of recombinant alpha and IFN-β therapy for the treatment of various disorders in recent years, cases of interferon-associated necrotic ulcers have been reported in the literature. Further studies are required to determine the potential role that inflammatory chemokines may play in the development of this rare side effect of IFN-β treatment. We report a case of extensive interferon-associated necrotic ulcers occurring at the injection site of a patient using subcutaneous IFN-β-1b for the treatment of MS.

Access this article online

Website: www.jrpp.net

DOI: 10.4103/2279-042X.155762

CASE REPORT

A 49-year-old female with relapsing-remitting MS received immune modulating therapy with recombinant IFN-β-1b, 8 million IU, by subcutaneous injection given alternately in thighs and arms every other day. In addition, baclofen, Amantadine were orally taken daily. After 3 months of interferon injections, erythematous patches and plaques developed at the injection sites and gradually progressed to areas of indurated erythema with central necrotic ulceration. Initially the lesions were transient, but after several weeks the erythematous skin at the site of the lesions became fixed. The lesions were painful. The patient did not exhibit fever, weight loss, arthralgias, or myalgias. She had no history of drug allergies. She denied any previous history of connective tissue disorders or other underlying coagulation or bleeding disorders. Skin examination revealed necrotic ulcers of 6–8 cm in diameter on both thighs and smaller necrotic ulcers on both arms [Figure 1]. There was no lymph node enlargement. Initially, she was diagnosed with cellulitis and treated with antibiotics, but when the lesions failed to resolve, she was referred to us. The differential blood count and the blood chemistry were within normal limits. Blood cultures were negative. Gram and periodic acid-Schiff staining were also negative. X-rays of both thighs and arms revealed no osteomyelitis. An ultrasound of the necrotic ulcer showed soft tissue edema without any fluid collections. Histological evaluation was conducted before treatment on the patient who had consented to a skin biopsy. Two deep skin biopsies were obtained from wedge from floor and margin altogether. They showed nonspecific inflammatory reactions including acantosis, hyperkeratosis, psudoepithelial hyperplasia, hyperplastic changes of blood vessels, and occasionally vessel thrombi with perivascular lymphocytic and neutrophilic infiltration [Figure 2]. No evidence of vasculitis and granulomatous reactions was seen. Direct immunofluorescence with staining for C3, IgG, IgA, and IgM was negative. We diagnosed the lesions as skin and soft tissue necrosis secondary to IFN-β-1b injection. Treatment consisted of stopping the subcutaneous IFN-β-1b injections and switching to a different IFN-β preparation that is injected intramuscularly once a week. She was also referred to a plastic surgeon for surgical debridement. Her arm ulcers were excised, and the sites were sutured closed [Figure 3]. The thigh lesions were left to heal by secondary intention after some suture repair to reduce the size of the wound areas. Strict wound care and skin grafting was also performed [Figures 3-5]. With this regimen, the patient's skin lesions improved over the course of the following year.

DISCUSSION

Interferons are natural glycoproteins that have antiviral, antiproliferative, and immune regulatory functions. There are several classes of interferons including interferon alpha, beta, and gamma. Interferons alpha and beta are used worldwide in the treatment of several diseases including MS.[5] Three IFN-β formulations are currently approved for the treatment of relapsing-remitting MS: Subcutaneous IFN-β-1b, intramuscular IFN-β-1a, and subcutaneous IFN-β-1a.[1] In general, all IFN-β formulations are well-tolerated. Furthermore, improvements in injection technique, adverse effect management, and patient education have contributed to greater patient compliance with treatment regimens.[6] However, the administration of IFN-β is associated with the risk of a variety of adverse effects.[7] The most common of these are flu-like symptoms and in patients who receive subcutaneous injections, injection-site reactions.[7] The side effects that have been reported can be divided into class-specific and agent-specific effects. Class-specific side effects of IFN-β include fever, myalgias, arthralgias, and influenza-like symptoms beginning 2–6 h after injection and abating within 24 h.[6] In addition, IFN-β-1b is associated with agent-specific side effects, particularly injection-site reactions.[6] These injection-site reactions are usually mild and self-limited, but in rare cases they may become more severe, and may sometimes necessitate the discontinuation of therapy. Injection-site reactions are not uncommon and are mostly seen in female patients. They normally manifest as localized erythema without induration that is not severe.[8] Severe skin reactions with necrotic ulceration are rare. The pathogenic mechanisms of the severe skin reactions are not fully understood. The pathologic mechanisms of immunologically-mediated necrotizing vasculitis and platelet-dependent thrombosis in the dermis, which are similar to the mechanism of action of IFN-β in terms of receptor sites and immunological outcomes, could be involved.[4] Some reports have suggested that the vasospastic effects of IFN-β-1b, along with small arteriolar thromboses located in the deep subcutaneous fat, may be responsible for necrosis.[9] More recently, Buttmann *et al*. demonstrated direct induction of local chemokine expression and associated immune cell extravasation caused by IFN-β in human skin biopsy specimens.[10] In a literature review, we identified nine cases in which complications of IFN-β treatment were related to the injection area, as they are in our study. These are summarized in Table 1.[9,11-17] The mean age of the subjects in these nine cases is 44 years (34–62 years); seven are women,

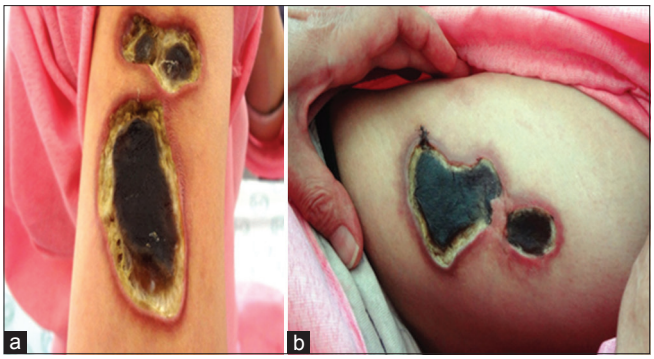

Figure 1: Severe necrotizing cutaneous lesions in the patient treated with interferon beta-1b. Necrotic skin ulcers with surrounding erythema were seen on the right arm (a) and on the left thigh (b)

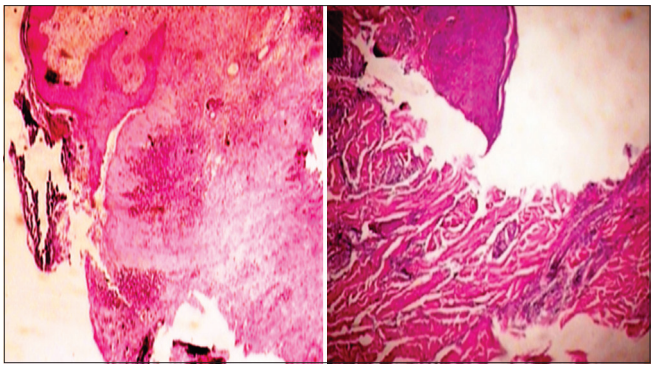

Figure 2: Histopathological finding of necrotic lesions associated with interferon beta-1b injection. Nonspecific inflammatory reactions without evidence of obvious vasculitis.

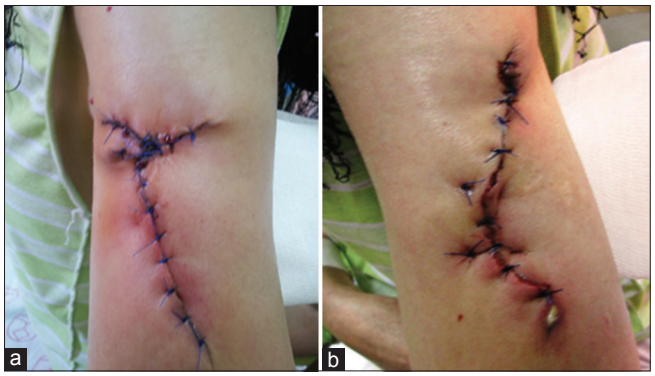

Figure 3: Primary closure of necrotic ulcer of right arm (a) and left arm (b) at the injection site after surgical debridement

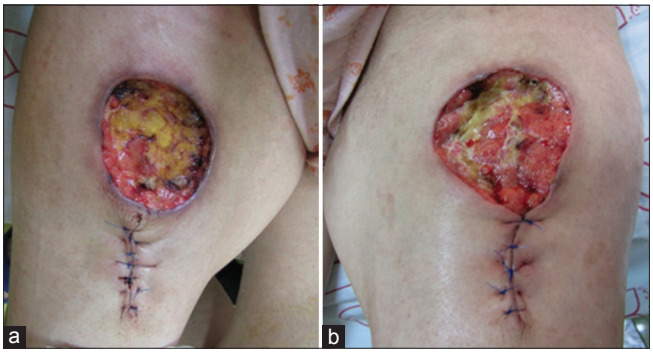

Figure 4: Surgical debridement followed by secondary intention of the interferon-associated necrotic ulcers, seen on the right thigh (a) and on the left thigh (b)

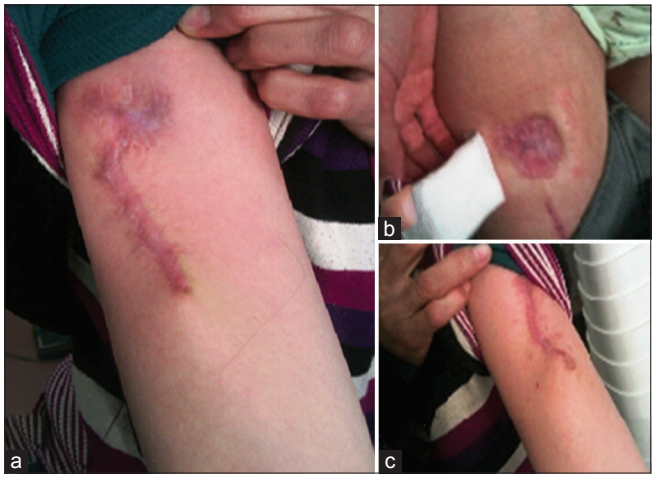

Figure 5: Wound healing at the injection site of interferon beta-1b: After 5 months, on arms (a and c), by suturing and on thighs by secondary intention scarring (b)

and two are men. The interval between beginning treatment with interferon and the appearance of symptoms ranges from 1 to 6 months, with a mean of 3 months. The areas most used for injections, the abdomen, and thighs, are the most common locations for the lesions. Our patient's lesions were on her thighs and arms, where she received her injections. In five of the reported cases, biopsy specimens were taken. In all five cases, lymphocytes were the main cell type in the lesions, which was also the case with our patient. The five biopsy specimens also showed perivascular dermatitis. In three of the biopsy specimens, there was thrombosis of dermal vessels.

It remains unclear exactly how IFN-β-1b therapy should best be handled. Switching from a subcutaneous to an intramuscular route of administration, diluting the preparation, and changing to an alternative type of interferon have all been advocated.[10] Rotating injection sites with each dose should also help minimize the risk of injection site necrosis. Finally, surgical interventions are cosmetically helpful and reduce wound management time.[9]

CONCLUSION

This case report demonstrates that ulcers associated with subcutaneous IFN-β-1b treatment should be considered in the differential diagnosis of patients with an ulcerated injection-site. A literature review

Table 1: Clinical and pathological characteristics of interferon associated cutaneous necrotic ulcer presented in previous reports

Author	Year	Age	Sex	Location	Onset of symptoms	Clinical appearance	Skin biopsy
Sheremata *et al.*[10]	1995	38	Female	Thighs	1 month	Necrotic ulceration	Perivascular dermatitis with lymphocytic infiltration and thrombosis of vessels
Feldmann *et al.*[11]	1997	34	Female	Thighs and abdomen	3 months	Necrotic ulceration surrounded by livedoid vascular pattern	Perivascular dermatitis with predominantly lymphocytic infiltration and leukocytoclastic vasculitis in reticular dermis
Weinberg *et al.*[12]	1997	42	Female	Abdomen	4 months	Necrotic ulceration	Not obtained
Weinberg *et al.*[12]	1997	52	Male	Thigh	3 months	Necrotic ulceration	Not obtained
Albani *et al.*[13]	1997	38	Female	Thighs and abdomen	3 months	Necrotic ulceration	Not obtained
Garcia *et al.*[14]	2001	44	Female	Thighs and buttocks	6 months	Nodular indurated erythema and necrotic ulceration	Perivascular dermatitis with predominantly lymphocytic infiltration and leukocytoclastic vasculitis in reticular dermis
Yang *et al.*[8]	2002	40	Male	4 limbs and abdomen	3 months	Necrotic ulcers surrounded by purpuric discoloration on	Arteriolar thrombosis located in deep subcutaneous fat
Casoni *et al.*[15]	2003	43	Female	Thighs, arms, and abdomen	2 months	Necrotic ulceration surrounded by painful erythema	Perivascular dermatitis with lymphocytic infiltration and thrombosis of deep vessels
Nakamura *et al.*[16]	2008	62	Female	Right thigh	4 years	Necrotic ulceration surrounded by painful induration	Not obtained
Our case	2012	49	Female	Thighs, arms	3 months	Necrotic ulceration surrounded by erythema	Perivascular dermatitis with lymphocytic infiltration no vasculitis

revealed that interferon-induced necrotic ulcers are a rare, but possible, complication of IFN-β-1b treatment. Neurologists need to be aware of the association between IFN-β treatment and severe skin reactions such as cutaneous ulceration and necrosis, and promptly refer patients who are developing skin lesions for further evaluation. Speedy and appropriate management of these side effects related to IFN-β treatment would greatly improve the adherence of MS patients to treatment, as would be taught a suitable method for self-injection by their physicians.

AUTHORS' CONTRIBUTION

Study concept and design: Gita Faghihi, Akram Basiri, and Bahareh Abtahi-Naeini. Case presentation: Gita Faghihi and Bahareh Abtahi-Naeini. Drafting of the manuscript: Mohsen Pourazizi, Ali Saffaei and Bahareh Abtahi-Naeini. Critical revision of the manuscript for important intellectual content: Akram Basiri, Bahareh Abtahi-Naeini, Mohsen Pourazizi and Ali Saffaei.

REFERENCES

1. Goldberg LD, Edwards NC, Fincher C, Doan QV, Al-Sabbagh A, Meletiche DM. Comparing the cost-effectiveness of disease-modifying drugs for the first-line treatment of relapsing-remitting multiple sclerosis. J Manag Care Pharm 2009;15:543-55.
2. Walther EU, Hohlfeld R. Multiple sclerosis: Side effects of interferon beta therapy and their management. Neurology 1999;53:1622-7.
3. Mokhtari F, Nikyar Z, Naeini BA, Esfahani AA, Rahmani S. Adverse cutaneous drug reactions: Eight year assessment in hospitalized patients. J Res Med Sci 2014;19:720-5.
4. Elgart GW, Sheremata W, Ahn YS. Cutaneous reactions to recombinant human interferon beta-1b: The clinical and histologic spectrum. J Am Acad Dermatol 1997;37:553-8.
5. Fragoso YD, Paggiaro MS, Mastromauro R, Jacondino Gda S, Wilson HM. Literature systematic review on the ophthalmological side effects of interferons. Arq Bras Oftalmol 2011;74:306-10.
6. Munschauer FE 3rd, Kinkel RP. Managing side effects of interferon-beta in patients with relapsing-remitting multiple sclerosis. Clin Ther 1997;19:883-93.
7. Bayas A, Rieckmann P. Managing the adverse effects of interferon-beta therapy in multiple sclerosis. Drug Saf 2000;22:149-59.
8. Gaines AR, Varricchio F. Interferon beta-1b injection site reactions and necroses. Mult Scler 1998;4:70-3.
9. Yang CH, Chen CH, Chan HL. Skin necrosis following a recombinant interferon-beta-1b injection. Chang Gung Med J 2002;25:774-7.
10. Buttmann M, Goebeler M, Toksoy A, Schmid S, Graf W, Berberich-Siebelt F, *et al.* Subcutaneous interferon-beta

injections in patients with multiple sclerosis initiate inflammatory skin reactions by local chemokine induction. J Neuroimmunol 2005;168:175-82.
11. Sheremata WA, Taylor JR, Elgart GW. Severe necrotizing cutaneous lesions complicating treatment with interferon beta-1b. N Engl J Med 1995;332:1584.
12. Feldmann R, Löw-Weiser H, Duschet P, Gschnait F. Necrotizing cutaneous lesions caused by interferon beta injections in a patient with multiple sclerosis. Dermatology 1997;195:52-3.
13. Weinberg JM, Wolfe JT, Sood S, Saruk M, Rook AH, Spiers EM. Cutaneous necrosis associated with recombinant interferon injection. Report of three cases with interferon beta-1b and review of the literature. Acta Derm Venereol 1997;77:146-8.
14. Albani C, Albani G. A case of cutaneous necrosis during interferon-beta 1b (B-IFN) therapy in multiple sclerosis. J Neurol Neurosurg Psychiatry 1997;62:418.
15. García-F-Villalta M, Daudén E, Sánchez J, Fraga J, Ramo C, García-Díez A. Local reactions associated with subcutaneous injections of both beta-interferon 1a and 1b. Acta Derm Venereol 2001;81:152.
16. Casoni F, Merelli E, Bedin R, Martella A, Cesinaro A, Bertolotto A. Necrotizing skin lesions and NABs development in a multiple sclerosis patient treated with IFNbeta 1b. Mult Scler 2003;9:420-3.
17. Nakamura Y, Kawachi Y, Furuta J, Otsuka F. Severe local skin reactions to interferon beta-1b in multiple sclerosis-improvement by deep subcutaneous injection. Eur J Dermatol 2008;18:579-82.

How to cite this article: Faghihi G, Basiri A, Pourazizi M, Abtahi-Naeini B, Saffaei A. Multiple cutaneous necrotic lesions associated with Interferon beta-1b injection for multiple sclerosis treatment: A case report and literature review. J Res Pharm Pract 2015;4:99-103.

Source of Support: Department of Dermatology, Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, **Conflict of Interest:** None declared.