

Cutaneous Ulceration Associated with Subcutaneous Interferon Beta 1a Injection

Subkütanöz İnterferon Beta 1a İlişkili Cilt Ülserasyonu

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ABSTRACT

Subcutaneous interferon beta 1a (IFN β 1a) has been shown to reduce relapse rates in patients with relapsing-remitting multiple sclerosis. We report the occurrence of severe necrotizing cutaneous reactions in a 19-year-old girl. She self injected IFN β 1a three times a week on the abdomen and both thighs. Treatment was initially well tolerated, but she described erythematous patches and local pain at the injection sites recently. The areas on the abdomen became violaceous with necrotic ulcers. Her therapy was changed to 0.5 mg fingolimod. The lesions began to improve and cicatrize after several weeks with postinflammatory hyperpigmentation. Early recognition of severe local adverse reactions and correction of the injection technique is important.

Key Words: Interferon beta 1a, Multiple sclerosis

ÖZ

Relapsing-remitting multiple sklerozda İnterferon beta 1a'nın (IFN β 1a) atak sıklığını azalttığı gösterilmiştir. Biz de 19 yaşında ciddi kütanöz cilt reaksiyonu olan bir olguyu sunmak istedik. Hasta haftada 3 defa karın ve her iki uyluktan IFN β 1a enjekte etmekteydi. Başlangıçta tedavi iyi tolere edilmişti fakat zamanla hasta enjeksiyon bölgelerinde kızarıklık ve lokal ağrı, sonrasında abdomende nekrotik ülserler oluştu. Tedavisi 0.5 mg Fingolimod ile değiştirildi. Lezyonlar düzelmeye ve haftalar içinde postinflamatuvar hiperpigmentasyon ile skatrize olmaya başladı. Lokal yan etkilerin erkenden tanınması ve enjeksiyon tekniğinin düzeltilmesi önem arz etmektedir.

Anahtar Sözcükler: İnterferon beta 1a, Multiple skleroz

INTRODUCTION

Multiple sclerosis (MS) is a severe demyelinating disease of the central nervous system characterized by autoimmune inflammation. Interferon is a biological molecule with antiproliferative, antiviral, and a variety of immunomodulatory effects. Treatment with recombinant interferon beta 1a (IFN β 1a) has been proven to reduce attack frequency and severity (1). However, IFN β therapy may be associated with a number of self-limiting transient systemic adverse reactions like flu-like symptoms, dizziness, arthralgia, lymphocytopenia, headache, weakness, and dizziness. MS patients may experience local skin reactions including pain, inflammation, and induration at the injection site during misguided subcutaneously injected IFN β 1b therapy. These reactions are observed in 20-60% of patients (2,3). In contrast, these skin reactions are not so common during IFN

β 1a treatment. Severe local reactions like thrombosis, mucinosis, lipoatrophy, dermal sclerosis, calcification, lupus erythematosus-like lesions, erythema nodosum, panniculitis, and necrosis are rare. We report a case with relapsing-remitting (RR) MS, who developed multiple cutaneous necrotic ulcers at the injection sides on the abdomen and both thighs due to subcutaneous (SC) IFN β 1a treatment.

CASE

A 19-year-old female was diagnosed with RR MS four years ago. Her family had accepted treatment two years after the diagnosis and she had started using IFN β 1a. She injected herself 22 μ g units IFN β 1a three times a week on the

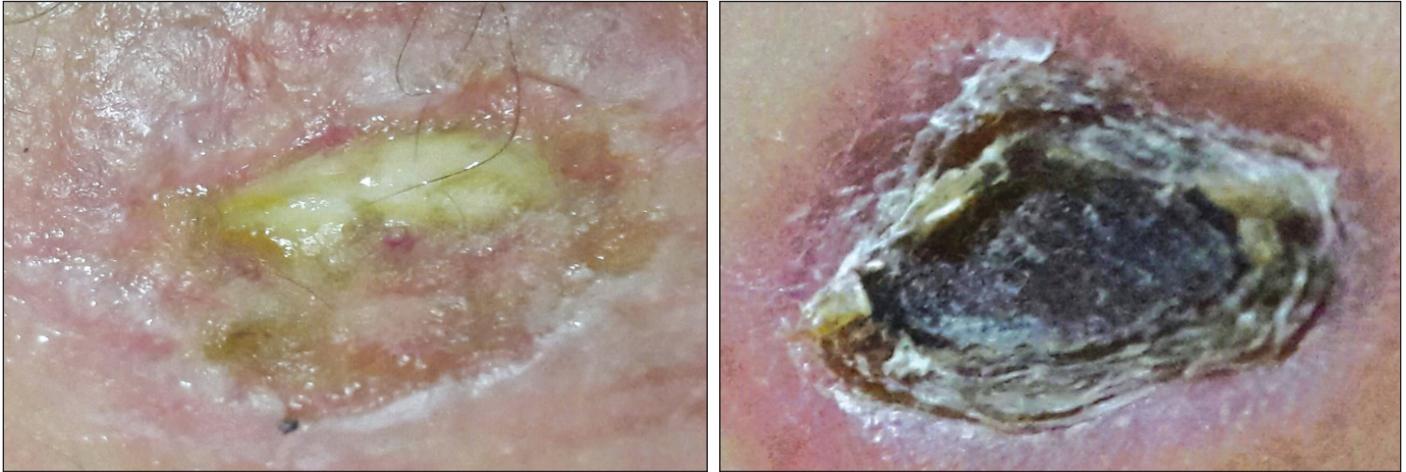


Figure 1: Necrotic ulcers and surrounding erythema.

abdomen and both thighs. During the 4 months of treatment, an optic neuritis attack occurred and the dosage was increased to 44 mcg. Treatment was initially well tolerated but in her detailed history she described erythematous patches and local pain at the injection sites. The areas on the abdomen became violaceous with necrotic ulcers 2 months ago. Physical examination revealed 5 different non-tender deep lesions 3-4 cm in length in the subcutaneous fat with surrounding erythema (Figure 1). Wound care, local anti-inflammatory gels and corticosteroids did not resolve the side effects. The lesions begin to improve and cicatrize after several weeks with postinflammatory hyperpigmentation. Her parents did not allow biopsy. Because of incompliance with treatment and a fear of injections in the previous 6 months, her treatment was changed to 0.5 mg fingolimod daily. No side effects were observed. She was followed up for 6 months without any attacks.

DISCUSSION

IFN β 1a and IFN β 1b are administered by either intramuscular (IM) or SC injection. Beer reported the incidence of necrosis with SC IFN β 1b as 4.8% and SC IFN β 1a as 3.2% after 1 year of follow-up. No patients on IM IFN β 1a experienced necrosis (4). The incidence of local reactions is dependent on the injection angle and depth. The reactions may occur years after treatment and resolve within several weeks. Skin necrosis after IFN β therapy in patients with MS was first reported by Sheremata et al. and biopsy specimens showed perivascular, interstitial lymphocyte infiltration and focal thrombosis of vessels (5). A placebo-controlled skin biopsy study revealed that inflammation at injection sites is due to chemokine expression by IFN β , resulting in T lymphocyte and monocyte extravasation (6). The pain soon after injection at the injection sites might be related to local vasospasm (7). There is some evidence about the presence of platelet activation in MS patients which could promote thrombosis (8). This immunological vascular side effect is unavoidable when the drug is injected into the dermis. Other

risk factors are the local infection of injection site, repeated use of the same area and improperly dissolved cold drug solutions (9,10). Correction of injection technique may help to prevent severe complications. If this precaution is not enough, termination of therapy is recommended. The superficial ulcers may improve with wound care. However, treatments such as antibiotics and intravenous steroids have been ineffective (11). Maintaining patients with MS on IFN β treatment can be challenging. These local side effects are reasons for missing doses or switching or discontinuing therapies. It has been reported that patients stopped IFN β treatment because of side effects after a median of 13 months which can lead to treatment failure (12). Selecting therapy with a lower risk for local side effects and education may help patients adhere to treatment. This case report should enhance awareness that severe local adverse reactions may occur and highlights the importance of early recognition and correction of the injection technique. Patients should be educated about the injection technique and local reactions associated with therapy.

REFERENCES

1. PRISMS (Prevention of Relapses and Disability by Interferon beta-la Subcutaneously in Multiple sclerosis) Study Group. Randomized double-blind placebo-controlled study of interferon beta-la in relapsing-remitting multiple sclerosis. *Lancet* 1998;352:1498-504.
2. Elgart GW, Sheremata W, Ahn YS. Cutaneous reactions to recombinant human interferon beta 1b: The clinical and histologic spectrum. *J Am Acad Dermatol* 1997;37:5538.
3. Lebrun C, Bertagna M, Cohen M. Cutaneous side effects of immunomodulators in MS. *Int MS J* 2011;17:88-94.
4. Beer K, Müller M, Hew-Winzeler AM, Bont A, Maire P, You X, et al. The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: An observational study. *BMC Neurol* 2011;11:144.
5. Sheremata WA, Taylor JR, Elgart GW. Severe necrotizing cutaneous lesions complicating treatment with interferon beta-1b. *N Engl J Med* 1995;332:1584.

6. Butmann 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.
7. Webster GF, Knobler RL, Lublin FD, Kramer EM, Hochman LR. Cutaneous ulcerations and pustular psoriasis flare caused by recombinant interferon beta injections in patients with multiple sclerosis. *J Am Acad Dermatol* 1996;34:365-7.
8. Sheremata WA, Jy W, Horstman LL, Ahn YS, Alexander JS, Minagar A. Evidence of platelet activation in multiple sclerosis. *J Neuroinflammation* 2008;5:27.
9. Albani C, Albani G. A case of cutaneous necrosis during interferon beta -1b therapy in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1997;62: 418-28.
10. Weinberg JM, Wolfe JT, Sood S, Saruk M, Rook AH, Spiers EM. Cutaneous necrosis associated with recombinant interferon injection. *Acta Derm Venereol* 1997;77:146-8.
11. Feldmann R, Low-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.
12. O'Rourke K, Hutchinson M. Stopping beta-interferon therapy in multiple sclerosis: An analysis of stopping patterns. *Mult Scler* 2005;11:46-50.