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Multiple necrotizing skin lesions due to glatiramer asetate injection

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Abstract

Nicolau's syndrome due to glatiramer acetate (GA) injection has been rarely reported. We report a 35-year-old woman with multiple sclerosis who presented with two necrotizing skin lesions due to consecutive subcutaneous GA injection. The patient was diagnosed with Nicolau's syndrome and treated with wound care. The lesions regressed slowly with a mild scarring. We discontinued GA treatment because of the recurrence risk of skin lesions. We think the syndrome has a good prognosis with conservative treatment; however, discontinuation of GA may be necessary especially in case of multiple skin lesions.

Keywords: Glatiramer acetate, necrotizing skin lesion, Nicolau's syndrome

INTRODUCTION

Glatiramer acetate (GA) is a well-tolerated first line treatment of multiple sclerosis (MS). Injection site reactions are common side effects of GA. These reactions usually include rash, pain and swelling while severe necrotizing skin lesions have rarely been reported.[1-3] Here, we report a patient who had two necrotizing skin lesions due to GA injections.

CASE REPORT

A 35-year-old woman, who had relapsing-remitting multiple sclerosis for ten years, was treated with interferon beta 1a in the first eight years of her disease. Moreover, she had hypertension and obesity in her past medical history. Since she had two relapses in last two years, INF-beta had been switched to subcutaneous glatiramer acetate (GA) and she had not had any disease activity afterwards. Although she was stabile neurologically, she was admitted to our hospital, because of two skin lesions, in June 2018 - two years after the beginning of GA treatment. She explained that these two lesions appeared after the last two injections, respectively. She described the process as follows: She had a brief intense pain at the injection site soon after the injections. Then erythema occurred within hours after injections at the injection sites and she photographed the lesions (Figure 1a). Afterwards livedoid and hemorrhagic patches occurred at these sites (Figure 1b, c). Finally, necrosis was observed (Figure 1d). The lesions' sizes were 10x8 cm and 2x3 cm, respectively. There was a close relationship between the lesions and the injection both in terms of time and localization. In addition, the patient did not accept the biopsy. Therefore, the skin lesions were thought to be associated with GA injection and skin biopsy was not performed. In line with the suggestion of dermatology, wound care was applied with cream containing triticum vulgare aqueous extract and ethyleneglycol monophenyl ether, 2-3 times daily. The lesions regressed with wound care over 17 months but a scar tissue was still existing (Figure 1e).

Upon the patient's request and consent, ocrelizumab treatment was started. The patient has been followed up under this treatment for 3 years without any problem.

DISCUSSION

Injected disease modifying therapies which include interferon beta preparates and GA may frequently cause cutaneous side effects. These side effects are generally mild and not serious such as local redness, pain, erythema, swelling and induration of skin. Severe cutaneous side effects, on the other hand, are especially known with interferon beta such as ulcerative and necrotizing skin lesions.[4,5]

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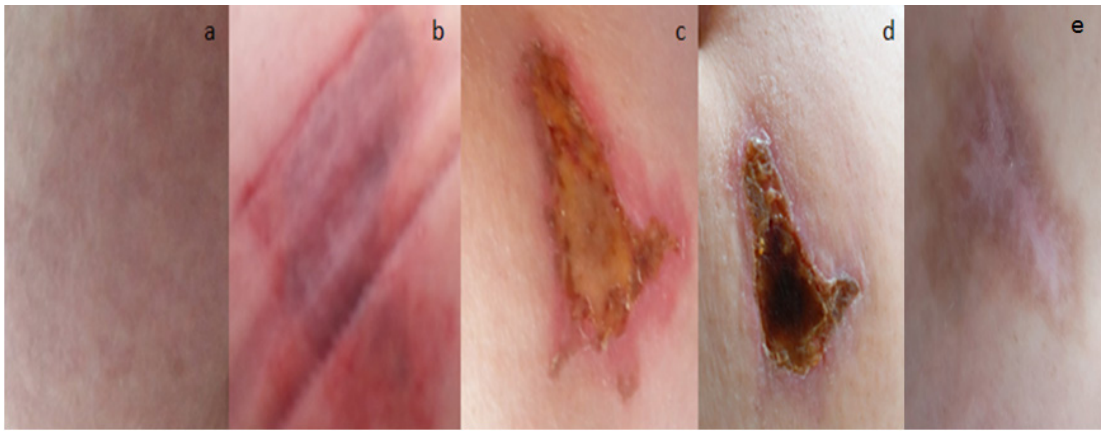

Figure 1. The evolution of the lesion due to Glatiramer acetate injection. Erythema occurred within hours after injection (a). Afterwards livedoid and hemorrhagic patches occurred (b, c). Finally, necrosis was observed (d). The lesion healed leaving scar tissue (e).

Only a few cases with severe skin reactions due to GA treatment have been reported in the literature.[6-8] The first was in 2003; reporting livedo-like dermatitis, also known as Nicolau's syndrome (NS), after injection of GA in a 33-year-old woman with MS.[1]

Nicolau's syndome or *embolia cutis medicamentosa*, is a rare complication of various intramuscular and occasionally subcutaneous drugs.[9] The onset is characterized by a pain immediately after the injection. Next, an erythema occurs at the site of injection within hours and a livedoid and a hemorrhagic patch occurs. Afterwards, necrosis of skin, subcutaneous fat and muscle tissue can be observed. The authors mentioned the importance of early treatment and the possible need for anticoagulation and surgery in such cases.[1]

Another case with NS was reported in 2007: a 59-year-old man with MS who had been treated with GA for six years.[10] The histopathological examination showed thrombotic occlusion of vessels and necrotic basal keratinocytes. The necrotic area was excised in the patient and the lesion improved in eight weeks. The authors reported that they continued to use GA.

Zecca *et al*. (2015), on the other hand, reported a patient who had recurrent NS due to GA injection.[11] The histopathological examination revealed thrombotic occlusion of small vessels in dermis, elevated epidermis, hemorrhage and inflammation in deep dermal layer and coagulation necrosis in dermal collagen and local fat tissue. So, even the pathogenesis of NS has not been clearly understood, authors suggested that the injection to the intra/peri-arterial or peri-venous region may induce severe pain and vasospasm which leads to local necrosis. Inflammation in the vessel walls may also contribute to necrosis.[9]

As seen from the case reports, there has been no standard treatment for NS. The treatment of NS due to GA is usually conservative.[1-3] Surgical intervention is suggested if tissue necrosis is present.[9] While some patients resolved completely, others had mild sequel. As for our patient, the lesions regressed slowly over 17 months with a mild sequel without any specific treatment.

As mentioned above, there are case reports indicating that GA treatment was continued after NS with no recurrence.[10] However, there was a case of recurrence in one patient after several years and thus the use of GA was cut.[11] In our case, we discontinued GA because the lesions occurred after two consecutive injections and our judgment was that the probability of recurrence might be high. Moreover, the patient indicated her preference of discontinuing GA treatment.

In conclusion, Nicolau's syndrome is a rare and severe cutaneous side effect of subcutaneous GA. These lesions seem to have a good prognosis with just conservative treatment. However, discontinuation of GA may be necessary especially in patients with multiple or recurrent skin lesions.

DISCLOSURE

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