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Necrotising cutaneous lesions as a side effect of glatiramer acetate

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Sirs:Glatiramer acetate (GA) is a synthetic drug, administered by daily subcutaneous injections, composed of the amino acids L-alanine, L-lysine, L-glutamic acid and L-tyrosine in a molar ratio of 4.2:3.4:1.4:1.0 for the treatment of relapsing-remitting multiple sclerosis (RRMS)[4, 5]. Reported side effects include local injection site reaction and transient systemic post injection reactions such as chest pain, flushing, dyspnea, palpitations and anxiety [2, 6, 10]. There has been one report of Nicolau's syndrome after GA injection [3], but to our best knowledge no cases of necrotising cutaneous lesions similar to the ones described with interferon have been reported until now.

We report two multiple sclerosis patients treated by GA who developed cutaneous necrotic lesions as an adverse effect of the treatment. The biopsy performed disclosed in both cases ischaemic cutaneous necrosis.

Case 1: A 38 year old woman with a six year evolution RRMS. Initially she was treated with subcutaneous interferon, which had to be interrupted owing to cutaneous adverse events (persistent cutaneous rash and vascular dermatitis), and she was changed to GA. Sixteen months after beginning GA treatment the patient developed several abdominal erythematous plaques, which turned to blisters over a lilaceous base surrounded by livedo reticularis, and finally became ulcerated in ten days (Figure 1). Biopsy revealed ischaemic necrosis of dermis and epidermis, with a lymphoplasmocytic infiltrate and blood extravasation in the reticular dermis among numerous thrombosed arterial vessels (Figure 2). Treatment was changed again, this time to azathioprine. Lesions healed over 2–3 weeks once treatment was interrupted.

Case 2: A 27 year old man with a two year history of RRMS was treated with daily subcutaneous GA. Eighteen months after starting treatment, he developed an erythematous painless plaque at the site of an injection, which became violaceous and ulcerous in one week. The biopsy disclosed the same findings as in the first case. Treatment was switched to Interferon beta 1-a. The lesion healed slowly over weeks.

Local injection site reactions are frequent in the treatment by GA. Most of them are mild and transient, and consist of pain, inflammation, induration, that occur in approximately 20–60% of patients[6]. Persistent localized lipoatrophy has also been described, [2, 7] which could be related to a subcutaneous panniculitis[10]. Severe necrotising cutaneous reactions have been widely described for all types of interferon, but to date these lesions have not been described for GA[8]. Nicolau's syndrome, a rare complication after intramuscular injection of certain drugs also named embolia cutis medicamentosa, has been recently reported after GA injection [3]. The suspected pathogenesis is the accidental intra-arterial injection of the drug, which leads to either acute vascular spasm or intravascular thrombosis, causing muscular and cutaneous necrosis[1]. The most prominent symptom is the acute intense pain following the drug injection, after a few minutes cyanotic patches and livedoid pattern develop. Although none of our patients suffered intense pain after GA injection, and the lesions developed over 1–2 weeks, a mild form of Nicolau's syndrome could be the cause of cutaneous necrosis in case 2. In case 1, a lesion occurred at several injection sites, therefore a drug-specific effect can be assumed.

Local thrombotic microangiopathy has been described as the cause of cutaneous necrosis following Interferon injection, potentially combining inflammatory and ischaemic local damage[9]. We here report similar pathological findings in the biopsy specimens of our patients sug-

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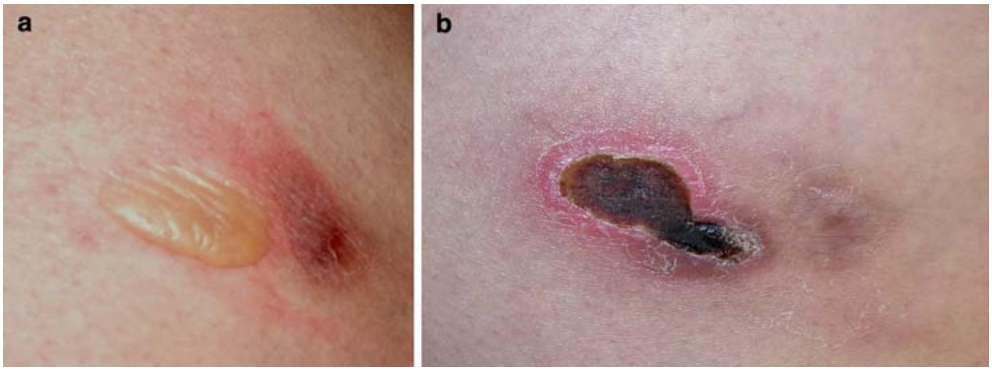

Fig. 1 **a**. Initial lesion formed by a bulla over an erythematous base. **b**. Necrosis and ulceration with surrounding livedo-pattern erythema

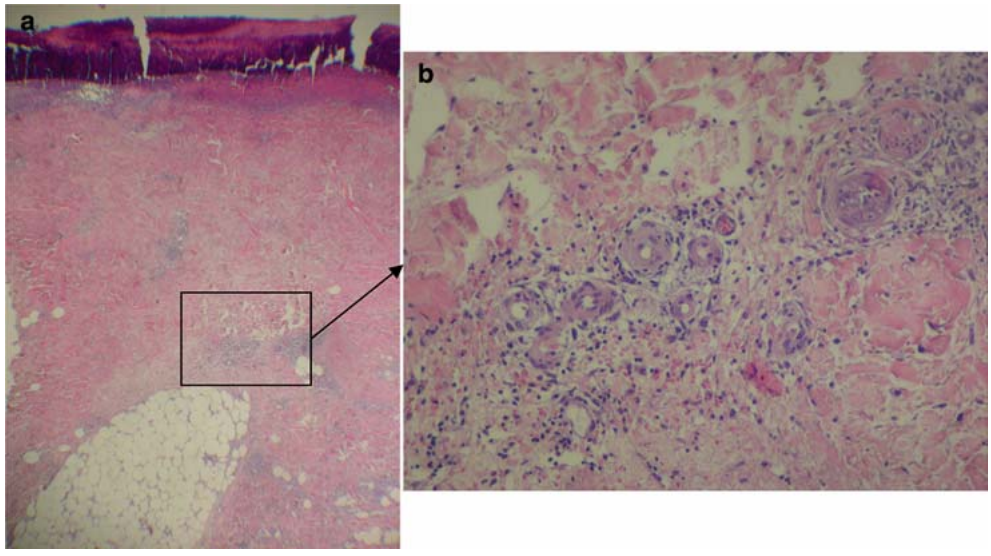

Fig. 2 a: 4 x haematoxiline-eosine. Fragment showing epidermic necrosis and scab, and deep dermic infiltrates. **b**: 40 x haematoxiline-eosine. Thrombus inside arterioles surrounded by limphocytic infiltrate and extravasation of erythrocytes in reticular dermis

gesting a similar mechanism for this potential severe adverse event linked to immunomodulatory therapies for multiple sclerosis.

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