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Letter to the Editor

Flare-up reaction in the inoculation drug sites by glatiramer acetate: First case described

Dear Editor,

Glatiramer acetate (GA) (Copaxone™) is an immunomodulatory drug used in multiple sclerosis (MS) to reduce the frequency of relapses.[1,2] It represents a safe treatment option with mild side effects. The pre-filled syringe contains 20 mg of GA and mannitol as excipient. GA is composed of the acetate salts of synthetic polypeptides containing L-glutamic acid, L-alanine, L-tyrosine and L-lysine, and may work as a decoy for the immune system.[1,2] There are described cases of hypersensitivity to GA as contact dermatitis, immediate and delayed exanthema and anaphylaxis, with positive skin tests in some of the cases.[2–4] Flare-up reactions are characterized by the reactivation of previously positive intradermal tests (IDT) or skin-prick-tests (SPT) elicited by patch testing or after systemic provocation with an allergen.[5] A case of flare-up reaction during provocation test with GA has been described in the skin test sites.[1] To our knowledge, we illustrate the first case of a patient with a flare-up reaction with GA in the inoculation drug sites.

A 37-year-old woman, diagnosed with remittent–recurrent MS and no history of atopic diseases is presented. She started treatment with subcutaneous injections of Copaxone™ 20 mg/day. From the first dose she immediately had a local erythema and inflammation of 2–3 cm along with pruritus in the injection site, disappearing spontaneously within 2–3 h. The eleventh day of treatment, 12 h after the GA administration, she displayed erythema, inflammation and pruritus in the gluteal area, arms, abdomen and legs, with no high fever detected, matching with the places where the patient had been administering herself the drug the preceding days. She took dexchlorpheniramine for two days and was referred to our outpatient clinic.

We observed persistent hot and erythematous plaques with painful subcutaneous nodules of 2–3 cm in each point of GA inoculation (Fig. 1A, B), we prescribed a treatment with oral antihistamines, topical corticosteroids and we recommended her to discontinue GA. Besides, a biopsy was obtained from the abdomen (Fig. 1A). One month later, the lesions disappeared without any residual lipoatrophy. We performed SPT and IDT on the volar side of the forearm with immediate, late and delayed lectures 12, 24 and 72 h later, either with GA and mannitol. The SPT with GA was made at a concentration of 20 mg/ml (1:1) and with mannitol at 200 mg/ml (1:1). The IDTs were carried out at 0.02 mg/ml (1/1000) and 0.2 mg/ml (1/100) with GA and at 2 mg/ml (1/100) and 20 mg/ml (1/10) with mannitol. We obtained negative results for mannitol and a negative SPT and IDT of 0.02 mg/ml for GA. However, we found an immediate positive result for GA with IDT of 0.2 mg/ml which remained positive for 4 days (Fig. 1C). The cutaneous testing with the described concentrations were negative in two non-atopic and two atopic controls.

The biopsy of the lesions showed a lobular panniculitis with lymphocytic venulitis and a significant eosinophilic infiltration in adjacent lobules and hypodermis, as well as thickening and inflammation of the septum (Fig. 1D–F). The patient's hemogram was normal with 190 eosinophils/mm^3 (3.4%). Also, in order to clarify the real involvement of this drug as the responsible of this unique clinical case, we performed a lymphocyte transformation test (LTT) to our patient and three sex- and age-matched controls, tolerating Copaxone™. The patient stimulation index (SI) was higher than the controls, for different concentrations of GA, being positive (SI > 2),[6] in two concentrations (10 and 5 μg/ml) (Table 1) despite the fact that the patient had started treatment with dimethyl fumarate (DMF) after we made the skin tests and before we performed the LTT. DMF has immunosuppressive and immunomodulatory activity, and GA just immunomodulatory activity. These actions of the drugs can explain the low SI in the patient, whether positive or not. Therefore, we diagnosed our patient of flare-up reaction triggered by GA. In our experience, a positive IDT-result at a concentration of 0.2 mg/ml does not seem irritating as previously reported.[7]

GA has the most favorable adverse effect profile compared with the other therapeutic options available for MS. The most common adverse effect of GA is a skin reaction at the injection site. In this immediate-type local reaction an IgE-mediated mechanism is probably involved.[7] It is also frequent, for approximately 20%–60% of the patients, to have pain, inflammation and induration at the injection site; these symptoms spontaneously disappear within hours or a few days. Up to 30% of patients have swelling at the injection site of GA, which ceases within minutes or hours. Subsequently, over time lipoatrophy can appear, and near 10% of patients have experienced at least one immediate-type systemic reaction.[8]

On the other hand, localized panniculitis at the sites of subcutaneous injections of GA for treatment of MS are considered a rare but distinctive side effect of this therapy, it is also said that it is underdiagnosed, appearing in up to 40% of the patients including those with lipoatrophy and no demonstrated panniculitis.[9,10] The histopathologic pattern of these lesions consists of a mostly lobular panniculitis, with histiocytes and T lymphocytes in the fat lobule and thickened septa with scattered lymphoid follicles, which are mostly composed of B lymphocytes.[1] The clinical and histopathological characteristics of drug-induced panniculitis are identical to others caused by different agents. All these cases were diagnosed

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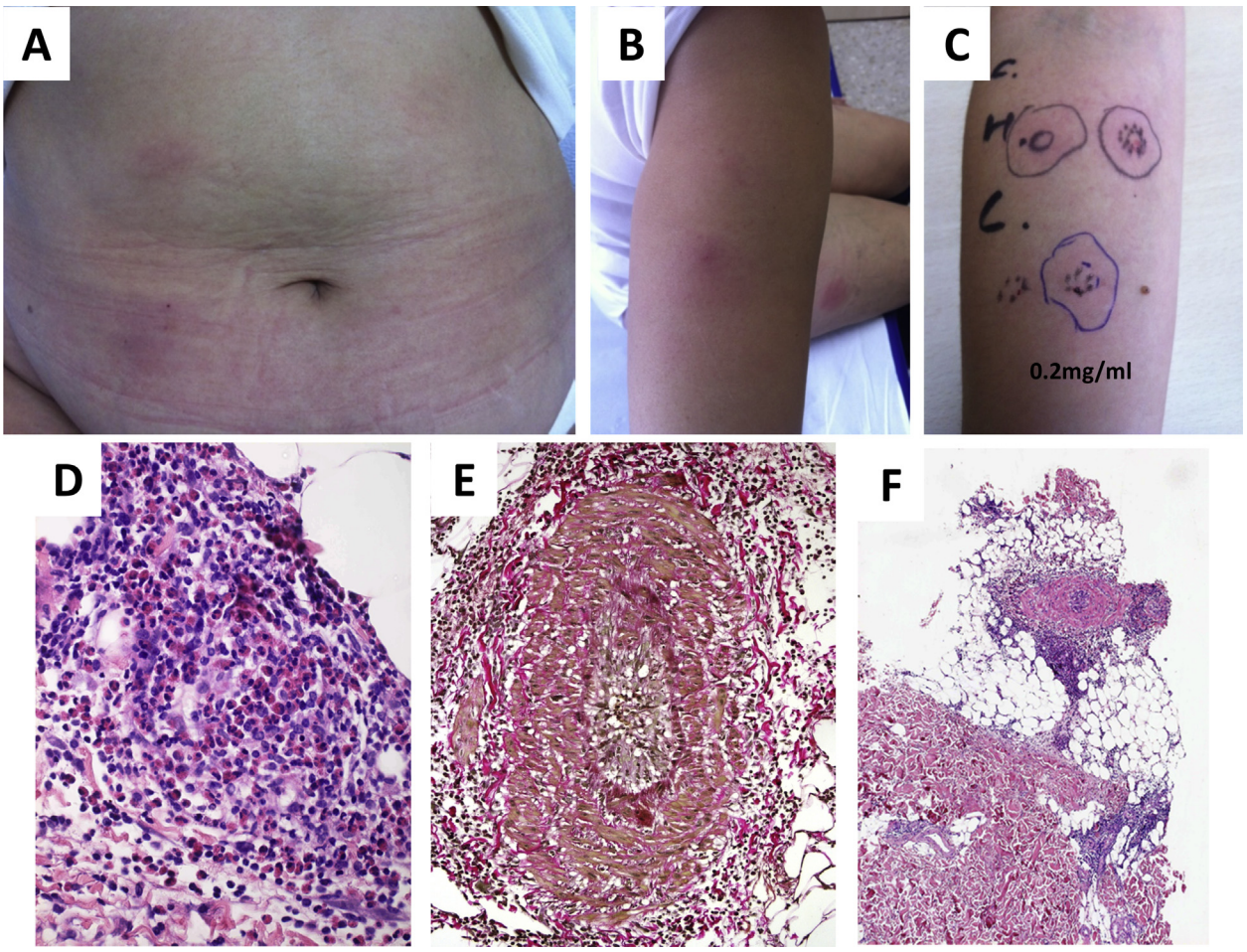

Fig. 1. **A**, **B**) Inoculation plaques on abdomen (biopsy taken from the bottom lesion) (**A**) and right arm and thigh (**B**); **C**) positive IDT of 0.2 mg/ml of glatiramer acetate; **D**) venous blood vessel with venulitis and a significant eosinophilic inflammatory infiltrate in adjacent lobules in hypodermis (hematoxylin and eosin stain, original magnification ×40); **E**) venous blood vessel with venulitis (elastica van Gieson stain, original magnification ×20); **F**) eosinophilic infiltration in hypodermis, septum and adjacent lobule (hematoxylin and eosin stain, original magnification ×10).

Table 1
Lymphocyte transformation test (LTT).

Glatiramer acetate	Stimulation index (SI)			
	Case	Control #1	Control #2	Control #3
25 μg/ml	1.83	0.81	1.46	nd
10 μg/ml	2.35	1.29	1.80	0.86
5 μg/ml	2.51	1.62	1.34	0.91
1 μg/ml	1.27	0.93	0.86	0.91
0.5 μg/ml	1.75	0.84	0.87	nd

nd, Not done.

according to a concordant history of drug intake and clinical improvement after drug withdrawal. Drug-induced lobular and mixed panniculitis, including eosinophilic panniculitis, have been rarely described. Our patient did not have a residual lipoatrophy and the pathological study of the biopsy illustrated an eosinophilic panniculitis caused by a flare-up reaction after repeated doses of GA (Fig. 1D–F).

To the best of our knowledge, we herein report the first case of allergic reaction to GA manifested as a flare-up reaction in the inoculation drug sites after treatment reported. This exceptional case has been confirmed either by cutaneous, histopathological and serological studies. Further investigation must be carried out in order to clarify its clinical relevance owing to the potential severity of reactions which GA may cause.

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Conflict of interest

The authors have no conflict of interest to declare.

María-José Sánchez-González [a,*], José Barbarroja-Escudero [a], Darío Antolín-Amérigo [a], Mercedes Rodríguez-Rodríguez [a], Laura Pericet-Fernández [b], Dolores Vélez [c], Teresa Bellón-Heredia [d], Melchor Alvarez-Mon [a]

[a] *Servicio de Enfermedades del Sistema Inmune-Alergia, Hospital Universitario Príncipe de Asturias, Universidad de Alcalá, Madrid, Spain*

[b] *Servicio de Dermatología, Hospital Universitario Príncipe de Asturias, Universidad de Alcalá, Madrid, Spain*
[c] *Servicio de Anatomía Patológica, Hospital Universitario Príncipe de Asturias, Universidad de Alcalá, Madrid, Spain*
[d] *Instituto de Investigación Sanitaria (IDIPAZ), Hospital Universitario La Paz, Madrid, Spain*

* Corresponding author. Servicio de Enfermedades del Sistema Inmune-Alergia, Hospital Universitario Príncipe de Asturias, Carretera Madrid-Barcelona Km 33.600, 28805 Alcalá de Henares, Madrid, Spain.
E-mail address: medicimj@yahoo.es (M.-J. Sánchez-González).

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