

Original Article

Patterns of local site reactions to subcutaneous glatiramer acetate treatment of multiple sclerosis: a clinicopathological study

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Abstract: *Background:* Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Glatiramer acetate (GA) is a commonly used immunomodulating drug. It is administered subcutaneously and is usually well tolerated; however, various local site reactions have been documented. *Objectives:* To characterize the clinical and histopathological patterns of local site reactions in patients treated with GA. *Patients and methods:* A retrospective case series of 12 patients with MS who experienced a local site reaction following treatment with GA. *Results:* We recognized 3 distinctive clinical patterns: early lesions with erythematous urticarial plaques and nodules (EPN) (75%), and late lesions: lipoatrophy (16.6%) and morpheiform plaques (8.4%). Biopsies revealed that the EPN lesions were characterized by superficial and deep infiltrate with eosinophils and some neutrophils, while the lipoatrophy showed sparse chronic inflammatory infiltrate with delicate fibrosis. The morpheiform plaque showed mixed inflammatory infiltrate and fibrosis. Seven patients applied clobetasole propionate ointment and then switched to tacrolimus monohydrate 0.1% ointment for up to a month. This treatment was beneficial for all patients with EPN. *Conclusion:* GA can cause a spectrum of injection site reactions that can be classified into 3 distinct patterns based on their time frame, clinical picture and histological pattern. Topical treatment with a potent steroid and tacrolimus cream can alleviate the EPN response.

Keywords: Local site reaction, glatiramer acetate, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system that affects approximately 1 million young adults worldwide. It is characterized by episodic neurologic symptoms that often lead to permanent neurologic deficits, which result in a gradual decline in both physical and cognitive abilities [1]. Although there are several forms of the disease, relapsing-remitting MS (RRMS) is the most prevalent form; it is found in 80% of patients [1]. RRMS has a female predominance and it typically begins around the second or third decade of life. The signs and symptoms of RRMS evolve over a period of several days, stabilize, and then often improve, either spontaneously or in response to steroid therapy. However, as the disease progresses, the steroid effect during

relapses diminishes [1-3]. Although there is no definitive cure for RRMS, several drugs have been shown to reduce the rate of relapses and the development of new brain lesions. These drugs are known as immunomodulatory agents and are available as first-line therapies for RRMS.

Glatiramer acetate (GA) (Copaxone®, Teva Pharmaceuticals Industries Ltd., Petah Tikva, Israel) is one of the most commonly used immunomodulatory drugs. It is a standardized, mixture of synthetic polypeptides consisting of L-glutamic acid, L-lysine, L-alanine, and L-tyrosine. By simulating myelin components, GA is believed to modify the cytokine profile involved in the inflammation, thus inducing the reactive Th2 immune-regulatory cells and resulting in a switch of the immune response from a Th1 to a Th2 inflammatory reaction. In addition, GA stim-

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Table 1. Patient demographics and course of MS disease

Patient Number	Age at GA initiation (years)	MS duration (years)	GA therapy duration (months)
1	51	23	121
2	53	NA	8
3	31	4	34
4	34	17	5
5	23	7	15
6	34	14	71
7	24	1.5	2
8	43	9	52
9	27	2	3
10	36	0.5	6
11	49	8	8
12	49	20	120

ulates the secretion of neurotrophin in the central nervous system, which may promote neuronal repair [2, 4, 5].

GA is administered subcutaneously once daily and is usually well tolerated; however, various adverse reactions have been documented [1, 6, 7]. Local site reactions are the most common adverse effects, occurring in up to 60% of patients treated with GA [6, 7]. Most site reactions are transient and disappear spontaneously within hours up to a few days; the reactions include localized erythema, induration, pruritus, and pain at the injection site [6-8]. However, serious chronic local site reactions, although rare, do occur and include sarcoidal granulomas, vascular thrombosis, subcutaneous sclerosis, panniculitis, and lipoatrophy at the injection site [9, 10].

The aim of this case series is to characterize the clinical and histopathological features of local site reactions in patients with MS who were treated with subcutaneous GA. New therapeutic options that diminish and even prevent local site reactions are also evaluated.

Patients and methods

This is a retrospective case series of 12 RRMS patients who were referred to the Dermatology Outpatient Clinic at the Sheba Medical Center because of a local site reaction to GA. In all cases, the referring neurologist, an MS expert with vast experience, considered stopping the treatment because of these adverse reactions.

The medical records of the 12 patients were reviewed. Data collected included the patients' demographics (age and sex), MS clinical history (duration, time elapsed from treatment initiation until skin reaction), clinical appearance and the course of the injection site reaction, histological findings, and response to treatment.

Injection site reactions were clinically defined as mild or severe. Mild reactions were defined as a transient phenomenon that lasted less than one week and resolved completely. Severe local site reactions were defined as either those that persisted for more than a week or those that resolved with skin changes, including hyperpigmentation, subcutaneous nodule, or lipoatrophy. The study was approved by the local ethical committee.

Results

From 1999 to 2011, twelve female patients with RRMS experienced a local site reaction after an injection of GA; they were referred to a dermatology consultant. The patients' characteristics are described in **Table 1**. The mean age at GA initiation was 38 years (ranging from 23-53 years). The mean duration of MS was 9.6 years (ranging from 6 months to 23 years) and the mean time of GA treatment was 37 months (ranging from 2 months to 10 years).

The clinical and pathological characteristics of the local site reactions are described in **Table 2** and shown in **Figures 1-3**. The time from the initiation of GA injections to the appearance of skin lesions varied widely from 1 week to 10 years, with an average of 21 months. The lesions were solely located at the injection site, which included the thigh, abdomen, arm, or hip. The most common site was the thigh: 7 out of 12 patients (58.33%). The second most common site was the abdomen 4 out of 12 (33.3%). Seven out of the 12 patients (58%) developed erythematous, edematous, tender somewhat indurated plaques, and nodules (EPN) (**Figure 1**) that became softer with time, although in some cases, a post-inflammatory hyperpigmentation remained. This type of reaction occurred within 4 months of the GA initiation. One patient (patient 1) experienced erythematous plaque that eventually developed into an atrophic firm plaque (morpheiform) 10 years after she started GA. Lipoatrophy was observed in 3 of the 12 patients (25%) that was preceded in 2 of them

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Table 2. Local site skin reaction, time of appearance, and clinical and histologic manifestations

Patient Number	Time until local site reaction appeared (months)	Clinical skin reaction	Histology type of local skin reaction*	Therapy for local site reaction
1	120	EPN and morpheiform	2	Clobetasol and tacrolimus
2	0.25	EPN	1	Clobetasol and tacrolimus
3	30	Lipoatrophy	3	NA
4	4	EPN	1	Clobetasol and tacrolimus
5	0.25	EPN	1	NA
6	2	EPN	NA	Clobetasol and tacrolimus for EPN
	59	Lipoatrophy		
7	1.25	EPN	1	Clobetasol and tacrolimus
8	0.25	EPN	1	Clobetasol and tacrolimus
9	0.25	EPN	1	NA
10	0.25	EPN	NA	NA
11	0.25	Lipoatrophy	NA	Clobetasol and tacrolimus
12	36	Lipoatrophy	NA	Clobetasol and tacrolimus

*Histology type 1 (EPN): Perivascular and interstitial dermatitis with eosinophils and neutrophils in various proportions, involving subcutaneous lobules with small foci of fat necrosis. Histology type 2 (Morpheiform plaques): Perivascular and interstitial dermatitis with many eosinophils and neutrophils in various proportions, and some plasma cells associated with thick collagen bundles and fibrosis. Histology type 3 (Lipoatrophy): Perivascular lymphocytic infiltrate with loss of subcutaneous fat tissue and partial replacement by delicate collagen bundles.

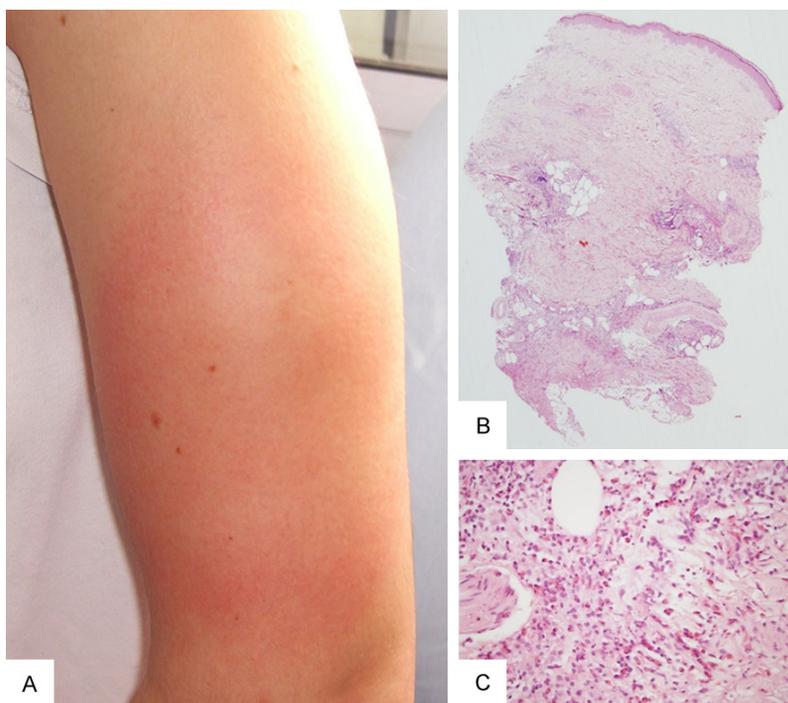


Figure 1. A. Erythematous edematous tender plaque (EPN) on the arm following GA injection. B. Biopsy specimen shows superficial and deep, perivascular and interstitial infiltrate (H&E×20) C. Dominated by eosinophils (H&E×400).

by a minimal inflammatory reaction and associated with a burning sensation. In one patient, the lesion appeared within a week following the injection, while the lesion appeared 2.5-3 years

after using GA in the other patients. In one patient, lipoatrophy followed EPN. Yet, while the EPN reaction started within the first two months of treatment, the lipoatrophy developed five years later.

Eight patients underwent a 4 mm punch biopsy from the injection site lesions, within 24 h to a week after the appearance of the reaction. The histopathologic findings varied and were classified into three groups that correlated with the clinical picture.

The details of each group are as follows:

Group 1 (EPN): Perivascular and interstitial dermatitis with eosinophils and few neutrophils was seen in 6 patients; In one patient a

marked involvement of the subcutaneous lobules with small foci of fat necrosis was observed (**Figure 1**). Interestingly, this patient clinically developed later lipoatrophy (**Figure 3**).

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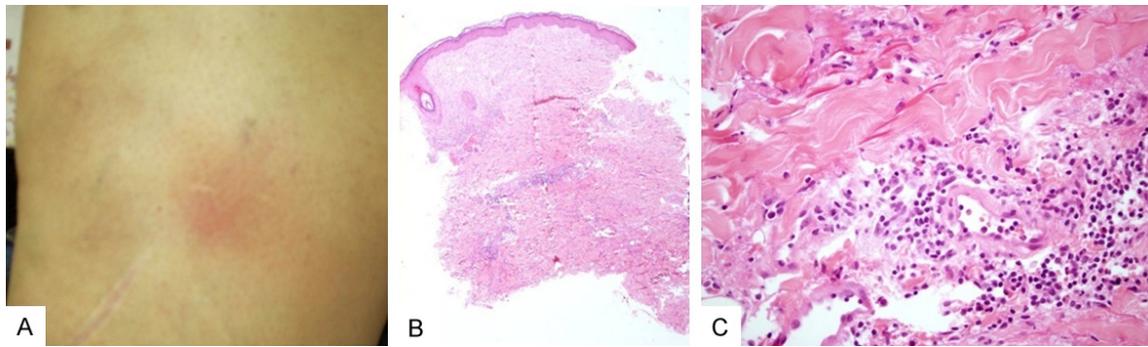


Figure 2. A. Erythematous tender nodule (EPN) of the thigh that developed following GA injection and hyperpigmented firm, slightly atrophic plaques developed later at the site of injection. B. Biopsy specimen shows superficial and deep, perivascular and interstitial infiltrate (H&E×40). C. Composed of eosinophils, plasma cell and lymphocytes accompanied by thickened collagen fibers (H&E×400).



Figure 3. A. Multiple lipoatrophy plaques on the thighs at the sites of injections. These lesions preceded by EPN. B. Hyperpigmented lipoatrophy plaque on the upper lateral thigh. C. Biopsy specimen shows sparse superficial and deep perivascular and periadnexal lymphocytic infiltrate (H&E×20). D. With replacement of the subcutaneous adipose tissue by delicate fibrosis (H&E×100).

Group 2 (morpheiform plaques): Perivascular and interstitial dermatitis with many eosinophils, some neutrophils and plasma cells associated with thickened collagen bundles and fibrosis (**Figure 2**).

Group 3 (lipoatrophy): Perivascular lymphocytic infiltrate with loss of subcutaneous fat tissue and partial replacement by delicate collagen bundles (**Figure 3**).

GA therapy was discontinued in five patients due to their skin eruptions: three with EPN, one with morpheiform plaque and two patients due to lipoatrophy.

Eight out of the 11 patients in our group were treated to alleviate the local site reaction and to enable the patients to continue with GA therapy; five of these patients had EPN, two had lipoatrophy, and one had a morpheiform plaque reaction.

Treatment was initiated before further injections of GA according to a unified protocol. Patients were instructed to spread clobetasole

propionate ointment (Dermovate, Glaxo) on the injection site a few hours prior to the GA injection and then twice daily in the following 3 days; the patients then switched to tacrolimus monohydrate 0.1% ointment (Protopic, Fujisawa GmBH) twice a day for at least a week up to one month depending on the response. Of the five patients with EPN who were treated with this protocol, three showed a very good response with disappearance of the lesions within a few days; in one of them, treatment was terminated shortly after commencement and there was no local site reaction in the following injections; two patients showed a mild response that manifested mainly as a decrease in the tenderness following the injection. The two patients who exhibited lipoatrophy and morpheiform plaque did not improve with this protocol. The treatment was not beneficial also in preventing further lipoatrophy in the one patient that the lipoatrophy was preceded by EPN.

Discussion

Local site skin reactions following a subcutaneous administration of various medications are

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not uncommon. Insulin, vitamin B12, vasopressin, antibiotics, methotrexate and growth factors, diphtheria, tetanus, and pertussis vaccines, and even acupuncture have been reported to induce local site skin reactions [11-19]. Reactions can vary in their time of appearance, clinical presentations, severity, and management. Most reactions are believed to be benign and transient, including erythema, localized urticaria, and tender nodule. However, severe chronic disfiguring lesions, such as granuloma, abscess, sclerodermoid reactions, vasculitis, thrombosis with emboli, skin necrosis, and lipoatrophy, although rare, have also been documented [11-20].

Injection site reactions to GA have been frequently reported in controlled studies that have assessed the efficacy and safety of the drug, although reports that describe the clinical presentation and the histology of these reactions are scarce [21-23]. Erythema, pain, inflammation, and pruritus are the most common adverse injection site reactions to GA, while severe site reactions are rarely seen [24].

In this case series, we describe the clinical and histopathological spectrum of local site reactions to GA and suggest therapeutic options to alleviate these reactions. Our study group of 12 female patients with RRMS was comparable to a study that showed female predominance and had a mean age of 39 ± 5 year [1].

We found that the mean duration of the MS disease at the time of GA initiation and the mean time of therapy with GA treatment were 9.6 and 1.75 years, respectively. This may reflect either a delay in diagnosis or a lag period in which the patient was either treated with other therapies or was not receiving any therapy at all.

The current study showed that the lag period from the initiation of GA therapy to the appearance of an adverse event could be divided into two separate time frames: immediate response and late response. The immediate response occurs from the first injection until 12 months after GA initiation; the late response appears at least one year after beginning treatment. In general, the time frames correlated with the clinical appearance and histology of the lesions. Immediate responses presented as erythematous and sometimes tender to painful urticarial plaques that resolved with time, rarely leaving

hyperpigmentation or a small firm nodule, while late responses resulted in either lipoatrophy or a morphea-like lesion with fibrosis. The presence of a clinically inflammatory stage in the late responses was recorded for 3 patients, one who developed a morpheiform plaque and two other who developed lipoatrophy. Unlike our other 3 patients who developed lipoatrophy, Soares et al. found that the primary lesion that later developed into lipoatrophy was an erythematous nodule [7]. Biopsy specimens from their group of patients showed panniculitis with marked inflammatory infiltrate. In one of our patients with lipoatrophy, biopsy showed moderate inflammatory infiltrate dominated by eosinophils involving the fat lobules and in the other biopsy did not show significant inflammatory infiltrate. This might be because the biopsy was performed late in the life of the lesion. This assumption is supported by the observation that both patients with the delayed permanent changes developed EPN-like lesions prior to the morpheiform plaque/lipoatrophy.

Based on our clinical and histological findings, along with previous reports, [6-8] we can distinguish between three types of histological responses:

EPN: Superficial and sometimes deep infiltrates that are rich in eosinophils, and compatible with an insect bite or urticarial-like reaction. This was more common as an early response that appeared a few months following initiation of therapy.

Morpheiform plaque: Perivascular and interstitial dermatitis with many eosinophils, neutrophils, and plasma cells associated with thick collagen bundles and fibrosis.

Lipoatrophy: Initially present as deep infiltrates rich in lymphocytes, neutrophils, eosinophils, and plasma cells, leading to a more chronic infiltrate, loss of subcutaneous adipose tissue and delicate fibrosis [6-8].

The latter two reaction patterns appear as a late response after more than one year of therapy.

While EPN is a limited, early (from initiation of GA) and immediate (following injection) response that has an allergic basis because eosinophils predominate and represents type 1 reac-

tion, [25] morpheiform plaque and lipoatrophy are late responses that carry a significant dysmorphic change at the site of injection, and probably represent a type 4 immune response. However, whether these patterns represent a spectrum of the same basic phenomenon as implicated by the common initial clinical presentation and histological findings, or they are completely different reactions remain to be elucidated. It is also unknown why some patients develop the late disfiguring lesions at the injection sites.

The issue of lipoatrophy merits a special mention. It seems that lipoatrophy appears in two different settings and time frames. One appears late and results from marked immune/inflammatory responses to the drug, as demonstrated in our patient and in previous reports, [7, 26] while the other develops after a short time, even following the first injection, and is not preceded by a significant inflammatory response. Thus, one may conclude that lipoatrophy can also result from either toxic effect or trauma, as has been reported following insulin injection [27].

The underlying mechanism by which a GA injection induces a skin reaction is still unclear, although several mechanisms have been suggested. The first mechanism is that its highly immunogenic features might induce the immune system at the site of the injection [6]. The second mechanism is that the repeated trauma to the fat tissue can induce reactions; a study showed that, following minimally invasive trauma, inflammatory cytokines, such as interleukin-1 beta, interleukin-6, and tumor necrosis factor alpha, were released from the adipose tissue. A third mechanism is that the response is an allergic reaction to the GA injection components, as was reported with insulin injections [25, 28-31].

A variety of treatment options have been suggested in the literature for injection site reactions [24, 32-34]. These treatments include placing ice on the injection site, antihistamines, and short-term oral steroids. All these modalities are based on the assumption that if one alleviates the inflammation, the symptoms will diminish and late, permanent adverse effects, such as lipoatrophy, can be prevented. Our protocol in which a potent topical steroid was followed by a topical tacrolimus proved itself effi-

cient in treating EPN lesions. Note that these lesions by nature were limited, probably more superficial, and had less inflammatory infiltrate. Whether using our protocol will prevent early lesions from developing into lipoatrophy or morpheiform plaques is an issue that needs to be addressed. However, in our limited experience, this protocol was not beneficial in these cases. Therefore, it is important to be aware that lipoatrophy or morpheiform plaques may possibly develop at the injection site of GA. These reactions should be identified early, and either treated vigorously or, preferably, the GA treatment can be terminated.

There are some limitations in our study. It was not randomized and the number of patients was small. Prospective large-scale studies are needed to evaluate the incidence of injection site reactions after GA with an emphasis on possible risk factors, preferred site of injection, and the benefit of using a preventive topical treatment.

In conclusion, GA can cause a spectrum of injection site reactions, which range from early lesions that are relatively superficial and limited, to late lesions that are relatively deep and show fibrosis or lipoatrophy. Topical treatment with a potent/superpotent steroid and tacrolimus cream can prevent and diminish the early reactions at the injection site and, thus, improve patient compliance with the GA treatment.

Disclosure of conflict of interest

None.

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