

area caused by a foreign body reaction to steel fragments from the weapon.

Our letter describes a new case of foreign body reaction to stainless steel wire 3 decades after implantation. In this patient the lesion resembled basal cell carcinoma. This case report is unusual in that the condition presented 30 years after implantation with no previous triggering injury. Foreign body reaction should be included in the differential diagnosis of any skin process that develops over a surgical scar, even if the process takes place many years after the operation.

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## Embolia Cutis Medicamentosa (Nicolau Syndrome) After Glatiramer Acetate Injection<sup>☆</sup>

### Embolia cutis medicamentosa (síndrome de Nicolau) tras inyección de acetato de glatirámico

To the Editor:

Injection-site reactions are some of the most common complications in subcutaneously administered treatments.

We report the case of a 31-year-old woman with no known drug allergies, a history of asthma and hidradenitis suppurativa, neither of which was being treated, and relapsing-remitting multiple sclerosis. For four-and-a-half years, the patient had been receiving treatment with daily subcutaneous injections of 20 mg of glatiramer acetate (GA, Copolymer-1, Copaxone, Sanofi-Aventis, Barcelona, Spain).

She visited the emergency department due to acute pain in the left buttock after an injection of glatiramer acetate; the patient had not experienced the pain with previous injections. There was a whitish plaque at the injection site that became erythematous and necrotic over the following 5 days.

Physical examination (Fig. 1) showed a reddish-gray, livedoid plaque on the left buttock, measuring approximately 3 cm, with geographic borders, a necrotic center, and a more intensely erythematous-violaceous border. On the caudal part of the lesion there was a deep, round, adherent scab measuring approximately 8 mm in diameter.

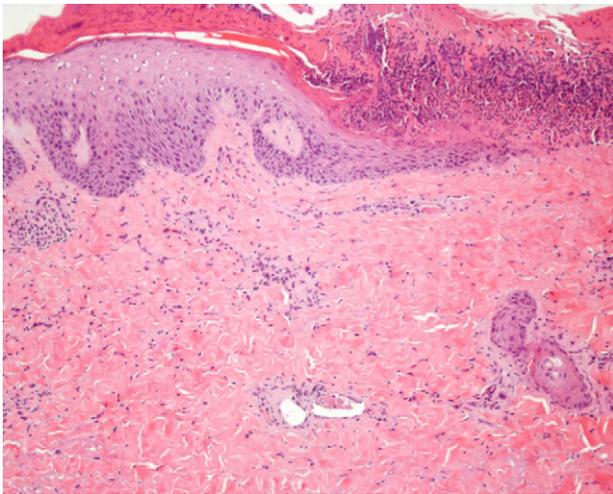
Questioning of the patient revealed that she complied with the injection protocol: the same injection site was not used in less than a week, the drug was left at room temperature 20 minutes before use, and the needle was placed in the correct position. Furthermore, the patient had continued to inject the treatment in the thighs and abdomen in the following days and no lesions had appeared at those sites. She reported a similar event in the same buttock a year earlier that had resolved without treatment and left an area of residual hypopigmentation.

A biopsy was performed of the peripheral area of the skin lesion on the buttock and showed a partially necrotic epidermis with coagulative necrosis of the dermal collagen, fat necrosis, and some fibrin clots in the small blood vessels (Fig. 2). Analyses, including a complete blood count, biochemistry with liver and kidney function tests, immunoglobulins, complement, antibodies to extractable nuclear antigens, antinuclear and anticardiolipin antibodies, and coagulation studies showed no relevant abnormalities.



**Figure 1** Violaceous livedoid plaque, with erythematous borders and a central scab located on the left buttock.

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**Figure 2** Epidermal necrosis corresponding clinically to the area of the scab, degeneration of dermal collagen, and fibrin clots in the lumen of the vessels of the superficial dermis (hematoxylin–eosin, original magnification x100).

These data led to a diagnosis of Nicolau syndrome. Topical treatment was instated with fusidic acid and betamethasone twice daily for 10 days; the lesion improved slowly and resolved within a month later, leaving a slightly depressed scar.

Glatiramer acetate is a mixture of synthetic polypeptides that is used to treat relapsing–remitting multiple sclerosis and has been shown to reduce the number of relapses of the disease and patient disability.<sup>1</sup> The most common adverse event is a reaction at the injection site, producing pain, inflammation, and induration; this occurs in 60% of patients and resolves within hours or days, leaving no residual lesion.<sup>2</sup> The rapid resolution of this event differentiates it from panniculitis at the injection site, which is less common, but nonetheless characteristic of glatiramer acetate. This is predominantly lobular panniculitis, which presents clinically as subcutaneous nodular erythematous lesions that resolve in 2 to 3 months and leave residual lipoatrophy in all cases.<sup>2</sup>

Nicolau syndrome, also known as livedoid vasculopathy or embolia cutis medicamentosa, was first described in 1924 by Freudenthal and then, in 1925, by Nicolau.<sup>3</sup> Gay-Prieto<sup>4</sup> reported a similar case in 1930. Nicolau syndrome after subcutaneous injection of glatiramer acetate was first reported by Gaudez<sup>5</sup> in 2003, and few similar cases have been published since then.<sup>6–8</sup> The pathogenic mechanism is not clearly understood, but accidental perivascular or intravascular injection of the drug appears to cause vasospasm and intravascular thrombosis, which gives rise to local skin necrosis due to ischemia.<sup>9</sup>

This is an unforeseeable but inevitable reaction, in which the injection technique plays a determining role; we also believe that it bears some relation to the drug administered, either due to its molecular weight or to the pH of the excipient used.

Because this reaction is mainly due to the injection technique and not to the drug itself, it should not contraindicate continuation of treatment.

Because the drug is administered daily, when the patient visited our department she had already administered 4 further injections after the appearance of the skin lesion and it was therefore logical to assume that this was not a reaction caused by an immune or allergic mechanism, as in this case the lesion would have recurred in the following days.

Because the patient is right-handed, the left buttock is the most inconvenient and inaccessible site for injecting the drug; the angle of injection or depth of administration of the drug may therefore have been incorrect.

After symptoms resolved and the patient had been advised not to inject in the buttocks, she continued with the same administration regimen and no new lesions had appeared at the injection sites a year after her visit to our department.

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## Acute Generalized Exanthematous Pustulosis Due to Milk Thistle (*Silybum marianum*) Tea<sup>☆</sup>

### Pustulosis exantemática generalizada aguda debida a una infusión de cardo mariano (*Silybum marianum*)

To the Editor:

Acute generalized exanthematous pustulosis (AGEP) is a rare disease that has been linked to certain drugs, such as antibiotics, antifungal agents, anticonvulsants, and antihypertensive agents.<sup>1-3</sup> Other possible triggers that have been described include infection, pregnancy, allergens, spider bites, iodinated contrast media, herbal medicinal products, and tumors.<sup>2</sup> In some cases, however, the causative agent cannot be identified.<sup>1</sup>

Several hypotheses that have been proposed to explain the pathogenesis of this skin reaction involve T lymphocytes and cytokines and posit that they are responsible for the characteristic neutrophilia and the aggregates of neutrophils in the histological picture of AGEP. It is recognized that previous sensitization, including contact sensitization, could explain some of these drug eruptions, and patch testing is positive in up to 80% of drug-related cases.<sup>4</sup>

A 45-year-old man with hyperuricemia on treatment with allopurinol for the previous 3 years consulted for an acute disorder that had started on the trunk 48 hours earlier and had spread to the face and limbs; he also reported fever and general malaise. Physical examination revealed erythema and edema of the skin of the face, trunk, and limbs—including the skinfolds and the palms—associated with multiple nonfollicular pustules (Fig. 1). There were also lesions on the oral mucosa and erosions on the lips. He did not report a history of infection and there had been no changes in the dose of his usual medication or new treatments added in the previous 3 months. However, he did remember taking milk-thistle infusions for a week before the onset of symptoms. The preparation, bought in a herbalist shop, contained dried seeds and was used by the patient to prevent dyspepsia. Histopathology of a lesion showed intraepidermal pustules, with edema of the papillary dermis and a predominantly neutrophilic perivascular inflammatory infiltrate. No acanthosis or papillomatosis was observed. The results of additional tests were as follows: white cell count, 16 500/ $\mu$ L (normal range, 4000-11 000/ $\mu$ L) (neutrophils,

10 000/ $\mu$ L [normal range, 2000-7500/ $\mu$ L]; eosinophils, 600/ $\mu$ L [normal range, 40-400/ $\mu$ L]; creatinine, 2.2 mg/dL (normal value, <1.1 mg/dL), and C-reactive protein, 256 mg/L (normal value, <12 mg/L). Culture of the pustules and blood cultures were negative. Serology for hepatitis B and C viruses, Epstein-Barr virus, and cytomegalovirus was negative. The patient did not recall having taken milk-thistle infusions previously, had no known drug allergies, and did not report any personal or family history of psoriasis. The findings of the medical history and of the additional tests were consistent with the clinical suspicion of acute generalized exanthematous pustulosis. Furthermore, the criteria proposed by Roujeau<sup>1</sup> were satisfied and, based on the validation scale proposed by the study group of the European study of severe cutaneous adverse reactions (EuroSCAR),<sup>2</sup> a definitive diagnosis of AGEP could be made. Treatment was started with oral prednisone at a dose of 0.5 mg/kg in a tapering regimen, in addition to emollients and fluid support. The clinical course was favorable, with resolution of the lesions and normalization of the complete blood count and renal function within 15 days. Patch testing was performed with the standard European series (Marti i Tor, Spain) 8 weeks after resolution of the condition. In addition, the hospital pharmacy prepared a 10% aqueous solution of the product supplied by the patient, which contained dried milk-thistle seeds. The results at 48 and 96 hours were positive (++) with an eczematous reaction at the site of application of the milk-thistle preparation. Other allergens in the patch tests were negative at the same time intervals. The results obtained with the same milk-thistle preparation in 10 control cases were negative. The patient has presented no further episodes after a year of follow-up.



**Figure 1** Multiple nonfollicular pustules on an erythematous, edematous base.

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