# Nicolau syndrome caused by Glatiramer

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**Declarations of Interest**
None.

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**Summary**

Injection-site reactions to glatiramer are common and include erythema, pruritus, pain, or induration. Additionally, the present systematic review of the literature documents 20 cases of Nicolau syndrome following glatiramer, a rare but potentially severe skin reaction. Abdomen and thighs are the most frequently affected areas (80% of reported cases), and permanent skin damage has been observed in 30% of cases. Recurrences are rare (<10%).

Dear Editor,

Embolia cutis medicamentosa, sometimes referred to as livedoid dermatitis or as Nicolau syndrome, is an uncommon complication of intramuscular, subcutaneous or, more generally, local injections *[Saputo and Bruni, 1998; Lardelli et al, 2020]*. This ischemic necrosis of the injected area results from the accidental intra- or para-arterial injection of a drug. The features of this distinctive injection-site reaction include immediate and severe local pain, followed by skin blanching and subsequent development of an erythematous macule that evolves into a livedoid patchy lesion. The lesion eventually becomes hemorrhagic and ulcerates, then heals over weeks to months, leaving often back an atrophic scar *[Saputo and Bruni, 1998; Lardelli et al, 2020]*. First reported after injection of bismuth, Nicolau syndrome is nowadays observed after administration of vaccines, local anesthetics, and particularly non-steroidal anti-inflammatory drugs and β-lactam antimicrobials *[Saputo and Bruni, 1998; Lardelli et al, 2020]*.

Cases of Nicolau syndrome have been observed after subcutaneous injection of glatiramer acetate *[Gaudez et al, 2003]*, an immunomodulator that is employed as a disease-modifying drug in the treatment of

relapsing-remitting multiple sclerosis and of clinically isolated syndrome *[Carter and Keating, 2010]*. To better characterize this association, we systematically collected the literature addressing this issue.

The subject headings terms "(embolia cutis medicamentosa OR livedoid dermatitis OR Nicolau[’s] syndrome) AND "glatiramer" were searched for without time and language limitations in the National Library of Medicine, Excerpta Medica and Web of Science databases. Secondary references and personal files were additionally assessed. Eligible were cases with the local symptoms and signs of Nicolau syndrome occurring abruptly after subcutaneous injection of glatiramer. From each included case, we extracted age, sex, site of injection, skin lesion size and the possible recurrence upon repeated glatiramer administration. A skin biopsy disclosing characteristic ischemic lesions was not a prerequisite for the diagnosis. For the final analysis, we retained 16 reports *[Gaudez et al, 2003; Bosca et al, 2006; Harde and Schwarz, 2007; Feldmann et al, 2009; Koller and Kränke, 2011; Martínez-Morán et al, 2011; Pulido Pérez, 2013; Samões et al, 2014; Dorado Fernández et al, 2015; Lobato-Berezo et al, 2015; Zecca et al, 2015; Mott SE et al, 2016; Kimbrough and Newsome, 2017; Blind et al, 2018; Vladhova et al, 2021; Demircan et al, 2020]* published since 2003 in English (N=10), Spanish (N=4) and French (N=2) from Spain (N=5), Germany (N=3), Austria (N=2), the United States of America (N=2), France (N=1), Portugal (N=1), Switzerland (N=1), and Turkey (N=1).

The reports described 20 multiple sclerosis patients (16 females and 4 males, 16 to 64 years of age) with Nicolau syndrome, which occurred after subcutaneous injection of glatiramer (table 1). Abdomen and thighs (N=16, 80%) were the most affected areas. This is not surprising, since these are also the most frequent injection sites of glatiramer. Of note, the clinically distinctive diagnosis of Nicolau syndrome was supported by a skin biopsy in 55% of cases. A permanent skin damage was observed in 30% of cases.

Glatiramer was again administered at least once in 12 of the 20 patients and a recurrence of Nicolau syndrome was observed in only one case *[Zecca et al, 2015]*.

Transient injection-site reactions to glatiramer are common and include erythema, pruritus, pain, or induration *[Kluger et al, 2009]*. The present systematic review of the literature documents cases of Nicolau

syndrome following glatiramer, a rare but potentially threatening injection-site reaction. There is a need to expand awareness of the very distinctive clinical presentation of Nicolau syndrome among healthcare professionals and patients, who auto-inject themselves with glatiramer.

## Authors' contributions

• Study concept: SAG Lava, MG Bianchetti.

• Study design and methodology: S Ciprian, SAG Lava, MG Bianchetti, PF Lardelli.

• Literature search and selection: S Ciprian, PF Lardelli.

• Data analysis: SAG Lava, GP Milani, D Consolascio.

• Writing – original draft: S Ciprian, SAG Lava.

• Supervision: Milani GP, Bianchetti MG, SAG Lava.

## Declarations of Interest

The authors have no potential conflicts of interest relevant to this study.


## Founding

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