

Sweet syndrome caused by sensitization to gabapentin

Patricia Rojas-Pérez-Ezquerro, MD^{a,b},
Blanca Noguerado-Mellado, MD^{a,b},
Mercedes Sáenz de Santamaría García, MD^{a,b},
Dasha Roa-Medellín, MD^{a,b},
Ignacio Hernández-Aragüés, MD^c, and
José Manuel Zubeldia Ortuño, MD, PhD^{a,b,d}



Clinical Implications

- We report a drug-induced sweet syndrome due to hypersensitivity to gabapentin confirmed by the positive patch test.

TO THE EDITOR

Sweet syndrome is a systemic inflammatory disorder characterized by the sudden onset of erythematous plaques, nodules, and painful erythematous papules, which typically shows an inflammatory infiltrate comprising mainly neutrophils in the dermis. The lesions can be accompanied by systemic symptoms such as fever and laboratory abnormalities. Sweet syndrome has traditionally been classified into 3 types: idiopathic or classic Sweet syndrome, malignancy-associated Sweet syndrome, and drug-induced Sweet syndrome.¹ Gabapentin (2-[1-(aminomethyl) cyclohexyl] acetate) is an antiepileptic drug whose anticonvulsive efficacy is lower than other new-generation antiepileptic drugs but shows a better safety profile. Hypersensitivity reactions to gabapentin are unusual,^{2,3} but we think that they are probably underreported.

We present the case of a 72-year-old man without a personal history of allergy, who developed acute nonpruritic, painless erythematous plaques on the dorsum of the hands (Figure 1). During the following 24 hours, they progressed to painful, indurated, erythematoviolaceous plaques with some superficial erosion. The plaques had a desquamative surface, and new lesions appeared on the arms, chest, neck, and knees in the form of asymmetrically distributed solitary erythematous plaques that were less intense than those on the hands. No mucosal involvement was noted. In addition, the patient had fever (maximum 38°C), a normal blood count without leukocytosis, and an elevated erythrocyte sedimentation rate of 59 mm/h. He was admitted to the hospital for study and treatment.

Associated malignancy, and autoimmune and infectious diseases were ruled out during admission. Additional tests did not show abnormal results: computed tomography of the body, serology for Epstein-Barr virus, cytomegalovirus, toxoplasma, and *Mycoplasma pneumoniae* were all negative, thus ruling out infection. Treatment was started with 6-methylprednisolone, and empirical treatment with meropenem and acyclovir was started. The patient's condition resolved gradually over the following 10 to 15 days. There were no residual lesions.

Approximately 15 days before the onset of symptoms, the patient had experienced mechanical lower back pain, which was

treated with a single dose of intramuscular dexamethasone and various anti-inflammatory drugs. The pain did not improve, and the patient's primary care physician decided to initiate treatment with gabapentin. The cutaneous symptoms started 5 days after starting the drug.

Under the suspicion of a drug-induced skin condition, gabapentin was disrupted. The patient's condition improved when this drug was discontinued and systemic corticosteroids were started.

Biopsy specimens taken during the episode revealed a dermal inflammatory infiltrate composed of neutrophils in the dermal interstitium with some neutrophil fragments, superficial edema, and a spongiform pustule in the epidermis without evidence of leukocytoclastic vasculitis. These findings were consistent with a diagnosis of neutrophilic dermatosis.

After discharge from hospital, the patient was referred to our Department of Allergy for evaluation, because the origin of his reaction was thought to be a drug-induced hypersensitivity mechanism.

Patch testing with readings at day 2 (D1) and day 4 (D2) with gabapentin 20% in dimethylsulfoxide (Nonweven Patch Test Strips Curatest; Lohmann & Rauscher International, Rangsdorf, Germany) yielded positive results at D2 (++++) and D4 (++++) (Figure 2), thus suggesting a type IV hypersensitivity mechanism. Patch tests in 5 healthy controls were negative.

In 1996, Walker and Cohen⁴ described the diagnostic criteria for drug-induced Sweet's syndrome, as follows: (a) abrupt onset of painful erythematous plaques or nodules, (b) histopathological evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis, (c) fever >38°C, (d) temporal relation between drug intake and clinical presentation, or recurrence after re-administration, and (e) resolution of lesions after drug discontinuation or treatment with systemic corticosteroids. After applying these criteria and taking into account the compatible symptoms, positive patch test results with gabapentin, and skin biopsy, we confirmed the diagnosis of Sweet syndrome caused by sensitization to gabapentin. A review of the literature to date reveals several cases of drug-induced Sweet syndrome,⁵⁻⁸ due to granulocyte colony-stimulating factor, tretinoin, trimethoprim/sulfamethoxazole, bortezomid, and azathioprine.^{9,10} However, to our knowledge, the case we report is the first involving hypersensitivity to gabapentin demonstrated by positive patch test.

Sweet syndrome was first described in 1964, although the pathophysiological mechanisms remain unclear. In addition, data on the hypersensitivity mechanism underlying drug-induced Sweet syndrome are scarce and the diagnosis is based on a compatible clinical picture, together with histopathology findings. The skin lesions are usually located on the upper limbs, especially the dorsum of the hands, and can also be found on the face and neck. In the case reported here, the lesions were initially located on the hands but afterward extended to the chest, neck, and limbs.

Nevertheless, multiple cases of Sweet syndrome resulting from sensitization to drugs have been reported.⁹ The potential pathogenic mechanisms in cases of Sweet syndrome include a type III hypersensitivity reaction, activation of T lymphocytes by antigens or superantigens, and alteration of neutrophil function, although none of these 3 mechanisms has been demonstrated consistently.



FIGURE 1. Erythematous plaques on the dorsum of the hands.



FIGURE 2. Positive patch test with gabapentin 20% in dimesylsulfoxide and negative control test with dimethylsulfoxide.

In our patient, the positive patch test results suggest a type IV hypersensitivity reaction to gabapentin. We believe that in all cases of Sweet syndrome, a standard allergy workup should be performed to identify the pathogenic mechanism and the culprit drugs for a more accurate diagnosis.

^aAllergy Service, Hospital General Universitario Gregorio Marañón, Madrid, Spain

^bGregorio Marañón Health Research Institute (IiSGM), Madrid, Spain

^cDermatology Department, Hospital San Pedro, Logroño, La Rioja, Spain

^dBiomedical Research Network on Rare Diseases (CIBERER)-U761, Madrid, Spain

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Corresponding author: Patricia Rojas-Pérez-Ezquerro, MD, Allergy Service, Hospital General Universitario Gregorio Marañón, 46th Dr Esquerdo St., 28007 Madrid, Spain. E-mail: patricia.rojas@salud.madrid.org.

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