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Patch test-proven delayed-type hypersensitivity from naltrexone/bupropion possibly eliciting psoriasis

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Exposure to certain medications can elicit or exacerbate psoriasis. However, there is limited evidence on the underlying pathophysiology leading to this association.¹ We report a case of patch test-proven delayed hypersensitivity from the anti-obesity drug naltrexone/bupropion, which elicited psoriasis.

Case Report

A 45-year-old woman with past medical history of class I obesity presented with an itchy rash, developing one day after starting a weight-loss drug, naltrexone/bupropion. The patient denied previous treatment with naltrexone or bupropion. She had been diagnosed with psoriatic spondylitis without skin involvement six years prior, in the setting of lower back pain in a patient with family history of psoriasis and negative HLA-B27. Thenceforth, she has been monitored in regular rheumatology consultations and managed with non-steroidal anti-inflammatory drugs and hydrotherapy. Physical examination revealed an erythematous maculopapular rash, on the trunk and upper limbs, without mucosal involvement. A drug reaction was suspected, therefore naltrexone/bupropion was discontinued and prednisolone 0.5 mg/kg/day was initiated. Two days later, the rash progressed to form multiple, non-follicular, pinhead-sized pustules, on an edematous disseminated erythema, extending to the face and lower limbs (Figure 1). The patient was admitted to the hospital. Acute generalized exanthematous pustulosis (AGEP) and generalized pustular psoriasis were considered, and a skin biopsy was performed. Cyclosporine 3 mg/kg/day and prednisolone 0.5 mg/kg/day were administered, with good response. Nevertheless, cyclosporine had to be suspended after one week due to dyspepsia and a *de novo* fivefold increase in liver transaminases. Histological assessment revealed subcorneal, spongiform neutrophilic

pustules, slight acanthosis with focal parakeratosis, and perivascular neutrophilic infiltration in the superficial dermis (Online supplemental Figure 2). After two weeks, the patient was discharged with prednisolone 0.25 mg/kg/day on a 2-month tapering plan. However, within a week, classic psoriatic plaques progressively developed on the limbs. The patient maintained the slow tapering of prednisolone and treatment with adalimumab was subsequently initiated, achieving an effective response on the skin and articular disease.

Patch tests were performed six months later with the commercialized drugs naltrexone/bupropion, naltrexone, and bupropion (each diluted at 30% pet.). Readings on day (D) 3 showed positive reactions to naltrexone/bupropion (++) and bupropion (++) (Figure 3A). The patient did not report any late reactions, including to naltrexone. Subsequent patch tests with different concentrations of commercialized bupropion (diluted at 1%, 5%, 10% and 20% pet.) resulted in positive reactions (Figure 3B). A biopsy of this reaction confirmed an allergic dermatitis (Online supplemental Figure 4). Control patch tests with bupropion 30% pet. were performed on ten healthy volunteers, yielding negative results.

Discussion

Psoriasis can be triggered or exacerbated by certain drugs. A direct effect is suspected for some medications, by inducing proinflammatory cytokine production.¹ Indirect mechanisms may also be implicated via Koebner phenomenon, in the case of drug hypersensitivity, allergic, irritant or photoallergic/phototoxic reactions.^{1,2} New drugs have been associated with psoriasis, particularly oncological and immunological targeted therapies.¹ Several cases of bupropion-associated psoriasis have been

reported, including one related to naltrexone/bupropion.³⁻⁵ However, the exact mechanism by which bupropion triggers psoriasis is unknown. Bupropion has also been documented to induce severe cutaneous drug reactions, such as Stevens-Johnson syndrome and AGEP.^{3,6,7}

Moreover, it is traditionally recommended against the use of systemic steroids in patients with psoriasis due to the risk of exacerbation, particularly with pustular or erythrodermic flares, after dose reduction or withdrawal. Nonetheless, recent data show a low rate of disease deterioration following systemic steroid exposure.^{8,9}

In our case, the rapid onset of a generalized pustular eruption within a single day of taking the first naltrexone/bupropion tablet, with a subsequent positive patch test, is strongly suggestive of AGEP. Nevertheless, the histological features in our biopsy favored the diagnosis of pustular psoriasis, particularly the absence of perivascular eosinophilic infiltration. In this case, clinicopathologic correlation was essential, considering that in an acute setting, the histologic differential diagnosis between these two entities is often difficult.¹⁰ Although we cannot exclude a plaque-type psoriasis flare in the setting of steroid tapering, we assumed that an initial AGEP caused by bupropion might have elicited an ongoing psoriasis as a result of Koebner phenomenon. To the best of our knowledge, this is the first report on a type IV hypersensitivity reaction to bupropion documented through patch testing.

Due to the obesity pandemic, a growing demand for weight-loss drugs has emerged. Furthermore, there is a known association between psoriasis and metabolic syndrome, a frequent diagnosis in obese patients.¹¹ Hence, special precautions may be taken when prescribing naltrexone/bupropion to patients with known history of psoriasis.

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Figure legends

Figure 1: Multiple, non-follicular, pinhead-sized pustules, on an edematous erythema, on the trunk, upper limbs and thighs.

Online supplemental Figure 2: Microphotograph showing a subcorneal and spongiform neutrophilic pustule, slight acanthosis with focal parakeratosis, and perivascular neutrophilic infiltration in the superficial dermis (H&E, x100).

Figure 3: Patch test readings on D3 showing a positive reaction to naltrexone/bupropion (++) and bupropion (++) , each 30% pet. **(A)**, and to increasing concentrations of bupropion **(B)**.

Online supplemental Figure 4: Microphotograph showing spongiosis and exocytosis of lymphocytes and polymorphonuclears into the epidermis. In the dermis, there is a perivascular infiltrate of lymphocytes and eosinophils (H&E, x100).











