Carbamazepine Hypersensitivity Syndrome Mimicking Mycosis Fungoides

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We report a case of a patient who experienced a generalized skin rash with systemic involvement 2 months after beginning carbamazepine treatment for trigeminal neuralgia. Skin biopsy specimens suggest mycosis fungoides. Complete remission of the clinical and pathologic changes after drug discontinuation and the positive result of carbamazepine from an epicutaneous test suggest a diagnosis of pseudolymphoma due to carbamazepine.

Carbamazepine is used to treat a variety of conditions, such as trigeminal neuralgia and some forms of epilepsy. Side effects include skin reactions with varying clinical and histologic expressions.[1-11] Pseudolymphoma, which rarely occurs,[12-14] appears as single, regional, or generalized lesions that may be caused by viruses, insect bites, or drugs. On clinical presentation, pseudolymphoma appears as benign, lymphohistiocytic proliferations that simulate malignant skin lymphomas when examined histologically.

We report a case of a patient who presented with systemic pseudolymphoma while receiving carbamazepine treatment for trigeminal neuralgia. On histologic evaluation, her skin lesions mimicked mycosis fungoides.

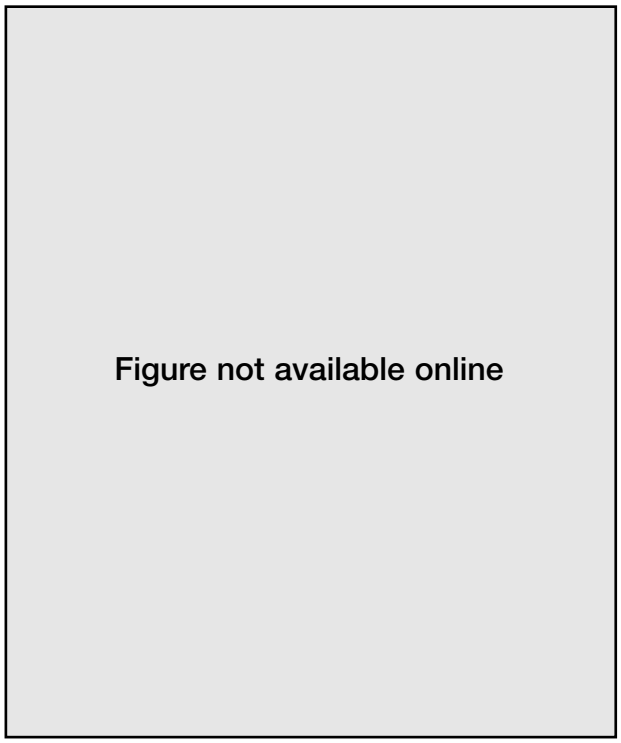

FIGURE 1. Fissures, desquamation, and facial edema.

Case Report

A 69-year-old woman had been taking flunarizine, hydrochlorothiazide, and amiloride for 1 year to treat her hypertension and had received carbamazepine for 2 months for the treatment of trigeminal neuralgia. A sudden, generalized rash with fever and malaise appeared 2 days after increasing her carbamazepine dose from 200 to 400 mg. Eight days after this outbreak, and in view of its persistence, she was referred to our Department of Dermatology.

On physical examination, the patient showed a generalized pruritic rash with maculopapular and vesicular lesions, patchy scaling, purpuric lesions on

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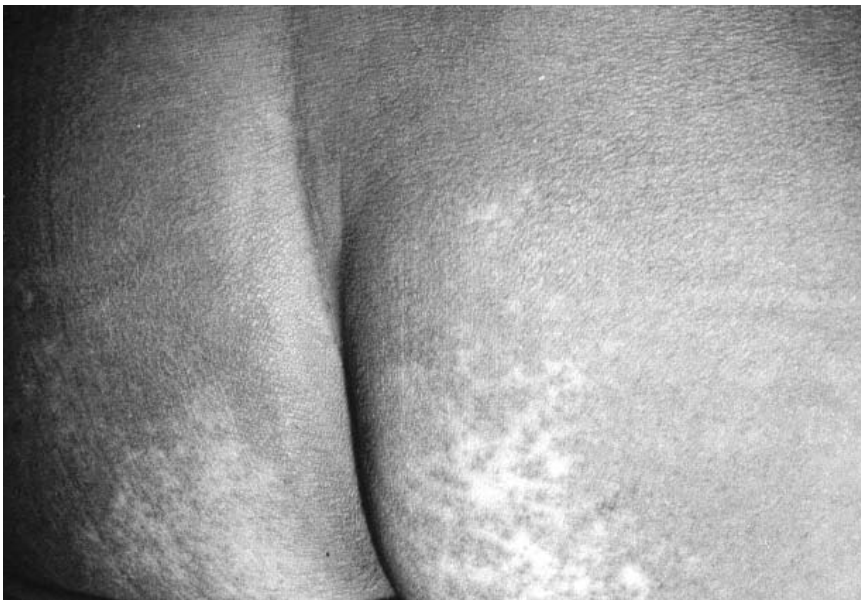

FIGURE 2. Confluent maculopapular rash.

the lower limbs, and facial edema (Figures 1 to 3). There were lesion-free areas within the rash and, although the lesions spread across the backs of the hands, they spared the surface corresponding to the metacarpophalangeal and interphalangeal joints. These skin symptoms were associated with fever, malaise, neurasthenia, and polyadenopathy.

Results of laboratory tests showed leukocytosis with marked monocytosis and lymphocytosis. The erythrocyte sedimentation rate and levels of transaminases, lactate dehydrogenase, alkaline phosphatase, b-2 microglobulin, IgA, and IgM were raised. Other tests that gave normal or negative results included hepatitis, syphilis, typhoparatyphoid fevers, brucella serology, autoantibodies, ultrasound, computed tomography, and radiologic examination. Normal distribution of the lymphocytic populations was documented in peripheral blood.

Examination of skin biopsy specimens showed a dense, banded, lymphohistiocytic infiltration in the papillary dermis that consisted mainly of atypical lymphocytes with kidney-shaped nuclei and strong tendencies to invade the epidermis and form accumulations inside the spongiotic vesicles (Figures 4 and 5). Isolated histiocytes and eosinophils were also found. Immunohistochemical stainings with UCLH-I markers for T lymphocytes and L-26 markers for B lymphocytes showed the band infiltrate in the upper dermis to be comprised of T lymphocytes. Cells inside the epidermal vesicles were also positive for the immunomarker UCLH-I. The L-26 marker for B lymphocytes gave negative results in both cases, and the study with direct immunofluorescence for IgA, IgG, IgM, IgD, κ, λ, and C_3 also showed negative results.

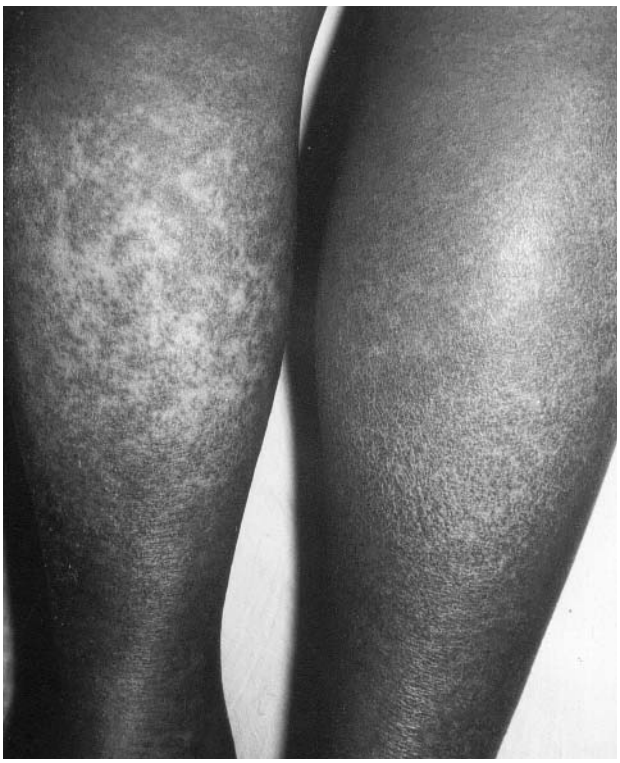

FIGURE 3. Erythematous and purpuric eruption over the lower extremity.

Improvement resulted when the carbamazepine treatment was discontinued, and it continued when oral prednisone was introduced. The lesions gradually subsided until, after 4 weeks, they had completely disappeared and the general status and analytic data returned to normal. Two years later, the patient remains asymptomatic.

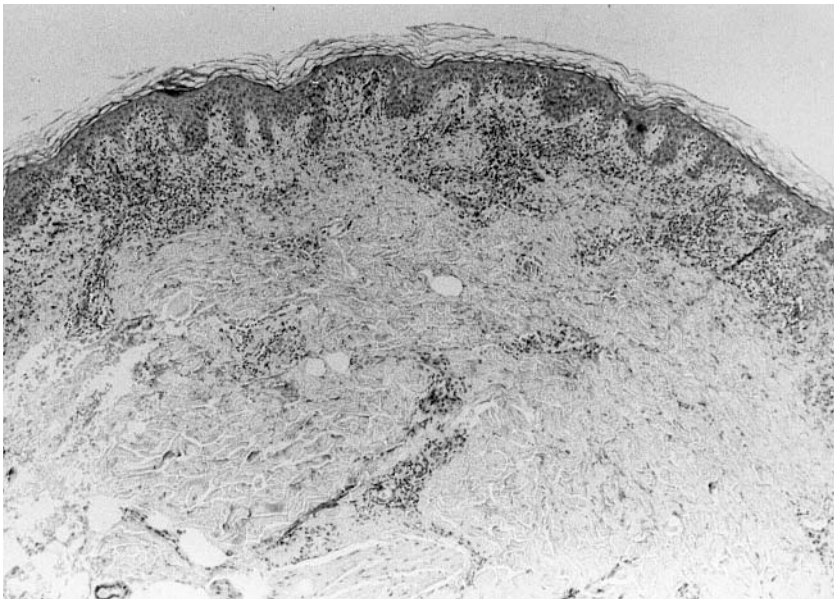

FIGURE 4. Dense, bandlike lymphoid infiltrate with exocytosis of lymphocytes and spongiotic vesicles within the epidermis (H&E, original magnification ×40).

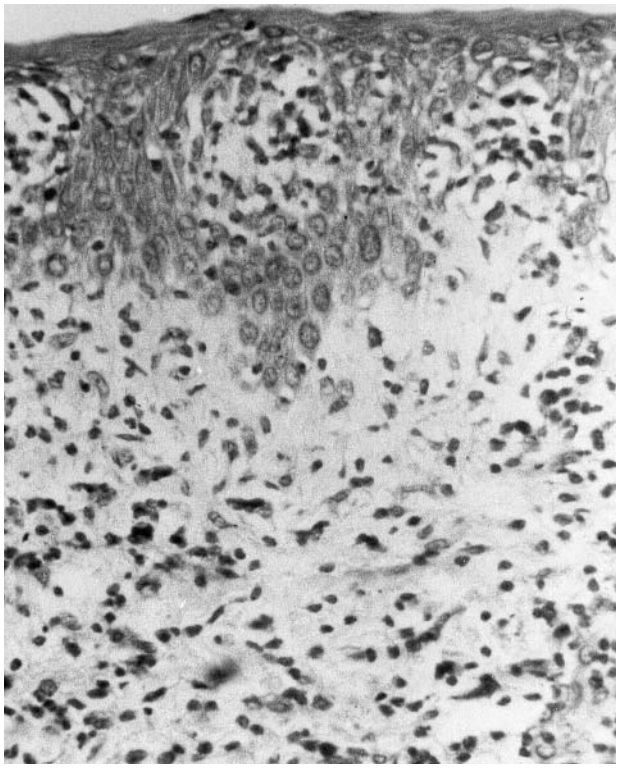

FIGURE 5. Bandlike dermal infiltrate and spongiotic vesicles (H&E, original magnification ×100).

Based on the clinical, analytic, histopathologic, and immunohistochemical data, and in view of the favorable progression of the condition with discontinuation of the drug, we suspected a pseudolymphoma due to carbamazepine hypersensitivity and performed an epicutaneous test to prove the sensitization. A patch test with the standard allergen battery gave negative results. We created special test groups by including 0.1%, 1.0%, and 2.0% carbamazepine in petrolatum, hydrochlorothiazide, amiloride, and flunarizine and obtained positive responses to the 3 concentrations of carbamazepine and negative responses to the rest of the allergens. A photopatch test with the battery of photoallergens and drugs previously mentioned gave negative results. A skin biopsy specimen of the positive reaction to carbamazepine was obtained and the histopathologic findings were very similar to those found in the clinical lesions. However, the spongiotic vesicles in the epidermis and the banded infiltrate in the upper dermis, which was later associated with eosinophils, were more prominent. Results of the immunohistochemical study showed that the cells forming the dermal infiltrate and the epidermal intravesicular cells were all T lymphocytes and positive for UCLH-I.

Comment

Carbamazepine is derived from iminostilbene, which is chemically related to the tricyclic antidepressants of the imipramine type. It is used in cases of epilepsy, particularly those with partial or single seizures, and in pain associated with trigeminal neuralgia. The most common adverse reactions, ranging from 34% to 56%, are neurologic and often dose dependent, but hematologic reactions are the most severe. At the dermatologic level, about 3% of patients show adverse reactions, including erythroderma,[1] toxic epidermal necrolysis,[2] Stevens-Johnson syndrome,[3] exfoliative dermatitis,[4] lichenoid rashes,[5] eczema and photodermatitis,[6] urticaria,[7] generalized pustulosis,[8] purpura,[9] maculopustular rash,[10] psoriasiform rash,[11] and pseudolymphoma.[12-14]

Phenytoin and its derivatives have been involved in the development of hypersensitivity reactions, which, in some particularly severe cases, are associated with multisystemic involvement (eg, adenopathies, fever, skin rash, hepatosplenomegaly) and with a specific histologic picture that mimics lymphomas (hence the name *pseudolymphoma*).[15] Cases of carbamazepine-induced pseudolymphoma, comparable to those described for phenytoin, have also been reported. However, lesions histologically mimicking mycosis fungoides have only been reported in 9 patients treated with phenytoin[13,16-21] and in 4 patients treated with carbamazepine.[12-14] Rijlaarsdam et al[13] reported 2 cases in which skin lesions appeared without systemic involvement, whereas the cases of pseudolymphoma reported by Welykyj et al[12] and De Vriese et al[14] appeared with systemic involvement and, on histologic examination, showed the skin lesions to mimic mycosis fungoides. Our case is the third to describe this type of presentation.

In many cases, it is histopathologically impossible to differentiate the spongiotic simulation from Pautrier's microabscesses of mycosis fungoides.[22,23] Nevertheless, in our patient and in the cases described by Ackerman,[22] the atypical cells forming the spongiotic site were more scattered and there was more spongiosis.

After completing a retrospective study of a series of patients with skin reactions to drugs, Callot et al[24] analyzed the differences between pseudolymphoma and the hypersensitivity syndrome and concluded that they are different conditions. The hypersensitivity syndrome due to anticonvulsants appears to be related to an allergic event, as deduced from a series of data[15] that included the following elements: the unnecessary need for an induction period after initial drug exposure except in the case of re-exposure when symptoms immediately reappear, the presence of the syndrome in only a small percentage of patients, lack of linear relationship with the dose, and immune mechanisms involved in demonstrating hypersensitivity by using the results of epicutaneous or blastic transformation tests. Hypersensitivity syndrome appears in the first 3 months after the onset of the treatment and is often preceded by fever and a variable, though often pruritic and maculopapular, skin rash that may progress to exfoliative erythroderma. Intense facial edema is an expected symptom and there may be an association with adenopathies, hepatosplenomegaly, immunosuppression and, occasionally, pharyngitis and conjunctivitis. The most common symptoms are changes in laboratory values for tests for leukocytosis with eosinophilia, atypical lymphocytosis, and high blood transaminase levels.[15] Although the origin of hypersensitivity syndrome is unknown, some authors suggest that carbamazepine behaves like an antigen and causes blastic transformation of the T lymphocytes.[18]

Epicutaneous test results have been useful for diagnosing cases of sensitization to carbamazepine[10,25]; however, the ideal minimum concentration has not been established. Concentrations of 1.0% and 5.0% have been recommended, and we, along with Terni and Tagami[6] and Duhra and Foulds,[26] have obtained good results using a concentration of 0.1% in petrolatum. Studies in which epicutaneous tests were used suggest that positive reactions are significant and indicate definite allergy to the drug. A negative reaction, however, cannot rule out sensitization—false-negatives may result if the tests are not conducted some time after the acute condition.[7] Results of the lymphoblastic transformation test are also useful in the diagnosis of hypersensitivity to carbamazepine.[7,27,28] An alternative therapy choice includes oxcarbamazepine, a ketoanalogue of carbamazepine.[26,27] Phenobarbital, phenytoin, and carbamazepine may be considered, but possible cross-reaction may occur.[28]

Clinicians and pathologists must take special care to recognize the heterogeneous clinical and histologic symptoms of these conditions. They must also consider the possibility of finding hypersensitivity syndrome to carbamazepine, which may histologically mimic mycosis fungoides and systemically present as a true lymphoma, as in our case. After drug discontinuation, complete remission of the condition, in addition to the results of carbamazepine allergy tests, will help clinicians make the correct diagnosis and, therefore, avoid unnecessary aggressive chemotherapy. Patients with carbamazepine hypersensitivity syndrome require regular follow-up examinations for years to prevent what is known as a pseudo-pseudolymphoma—a diagnosis of pseudolymphoma which, in time, becomes true lymphoma.[29]

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