Acute Generalized Exanthematous Pustulosis as a Manifestation of Carbamazepine Hypersensitivity Syndrome

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Abstract
Anticonvulsant hypersensitivity syndrome (AHS) is a multisystemic disorder involving cutaneous changes and typical blood abnormalities that can be triggered by aromatic anticonvulsant drugs. The syndrome is commonly associated with a macular or papular rash or erythroderma. Acute generalized exanthematous pustulosis is a very rare cutaneous manifestation of AHS.

A 41-year-old man was referred to our hospital for evaluation of a 3-day history of fever, leukocytosis, and generalized skin eruption. The patient had been taking carbamazepine for 1 month to treat hand tremor following surgery for intracerebral hemorrhage. Physical examination revealed facial edema and a large number of variable-sized pustules covering the body. Initial laboratory testing showed peripheral blood eosinophilia and abnormal liver function. A biopsy of pustular lesions revealed intraepidermal pustules, with perivascular lymphocytic infiltration. The skin lesions and laboratory results improved after withdrawal of carbamazepine and treatment with oral corticosteroids.

Keywords: Carbamazepine. Drug hypersensitivity.

Resumen
El síndrome de hiperensibilidad a anticonvulsivantes (SHA) es un desorden sistémico que incluye cambios cutáneos y alteraciones hematológicas típicas que pueden desencadenarse por fármacos anticonvulsivantes aromáticos. Este síndrome se asocia frecuentemente a erupción macular o papular o eritrodermia. La pustulosis exantemática generalizada aguda es una manifestación cutánea de SHA poco frecuente.

Un varón de 41 años de edad fue referido a nuestro hospital para evaluar una historia de fiebre, leucocitosis y una erupción cutánea generalizada de 3 días de evolución. El paciente llevaba un mes de tratamiento con carbamazepina para tratar un temblor de manos secundario a una cirugía por una hemorragia cerebral. La exploración física reveló un edema facial y un gran número de pústulas de tamaño variable cubriendo el cuerpo. El análisis de sangre inicial mostró eosinofilia periférica y alteraciones de la función hepática. La biopsia de las lesiones demostró pustulas intradérmicas, con infiltración linfocítica perivascular. Las lesiones cutáneas y los resultados del laboratorio mejoraron tras eliminar la carbamazepina y el tratamiento con corticoides orales.

Palabras clave: Carbamazepina. Hipersensibilidad a medicamentos.

Introduction
Anticonvulsant hypersensitivity syndrome (AHS) is a life-threatening drug hypersensitivity reaction characterized by fever, rash, lymphadenopathy, and hepatitis. It has also been associated with leukocytosis and eosinophilia [1]. The syndrome can be triggered by any of the aromatic antiepileptic drugs phenytoin, carbamazepine, or phenobarbital [2,3].

Acute generalized exanthematous pustulosis (AGEP), a very rare manifestation of AHS, is a severe skin eruption usually induced by drugs. Antibiotics have been most frequently associated with this condition, and more rarely carbamazepine [1,4,5].
We present the case of a patient who, following carbamazepine treatment, developed AHS with major cutaneous manifestations which are not common in the context of this syndrome.

**Case Description**

A 41-year-old man presented with an acute, severe febrile skin eruption in association with hypereosinophilia and hepatitis. The patient had been taking carbamazepine for 1 month to treat hand tremor following surgery for intracerebral hemorrhage. Physical examination revealed facial edema and a large number of variable-sized pustules covering the body (Figure 1). Laboratory test results revealed hypereosinophilia (white blood cell count, 16 560/mm³; 7% eosinophils; 14% atypical lymphocytes); a serum glutamic oxaloacetic transaminase level of 105 IU/L (normal, 10-35 IU/L); a serum glutamic pyruvic transaminase level of 187 IU/L (normal, 0-35 IU/L); a total bilirubin level of 1.4 mg/dL (normal, 0.2-1.2 mg/dL); a direct bilirubin level of 1.3 mg/dL (normal, 0.0-0.5 mg/dL); a γ-glutamyltransferase level of 368 U/L (normal, 8-53 U/L); a blood urea nitrogen level of 8 mg/dL (normal, 8-26 mg/dL); a creatinine level of 0.8 mg/dL (normal, 0.6-1.2 mg/dL); and a C-reactive protein level of 8.1 mg/dL (normal, 0-0.5 mg/dL). Serologic tests for antinuclear antibodies, antiDNA antibodies, and various viral antibodies were all negative. A skin biopsy of the patient’s neck and forearm revealed parakeratosis, pustules in the epidermis, and perifollicular lymphocytic infiltration in the dermis (Figure 2).

In view of the clinical and histologic changes observed, we considered that the patient’s condition was related to carbamazepine use. We consequently withdrew the drug.

<table>
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<tr>
<th>Table: Laboratory Values and Clinical Characteristics By Admission Day</th>
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<tr>
<td>Body temperature, °C</td>
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<td>White blood cell count, mm³</td>
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<td>Eosinophils, mm³</td>
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<td>Atypical lymphocytes, mm³</td>
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<td>Aspartate aminotransferase, IU/L</td>
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<td>Alanine aminotransferase, IU/L</td>
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<td>Prednisolone, mg/d</td>
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and admitted the patient to hospital for observation. The skin lesions resolved with treatment with oral prednisolone (starting dose, 30 mg/day) and the laboratory values also improved (Table). Fortunately, the patient’s hand tremor ceased without requiring further treatment with other medication. We recommended valproic acid as an alternative drug in the event of recurring hand tremor.

Discussion

The patient reported here presented with a severe febrile skin eruption in association with systemic involvement including hepatitis and eosinophilia following carbamazepine intake. The clinical manifestations and laboratory abnormalities were suggestive of AGEP associated with carbamazepine-induced AHS and confirmation was obtained by skin biopsy.

AHS was first described by Chaiken et al [6]. The syndrome is characterized by adverse effects caused by aromatic antiepileptic drugs such as phenytoin, carbamazepine, phenobarbital, and primidone [2,3]. It is an unpredictable and potentially severe reaction with a prevalence of between 1 in 1000 and 1 in 10,000 exposures [7]. Other drugs such as lamotrigine, captopril, mexiletine, sulfonamide, dapsone, minocycline, terbinafine, azathioprine, allopurinol, and antiviral agents have also been associated with AHS [8]. Clinical manifestations include fever, skin rash, and internal organ involvement such as hepatitis, myocardiitis, interstitial nephritis, and interstitial pneumonitis. Lymphadenopathy and hepatosplenomegaly may also be present, and more rarely, pericarditis, myocardiitis, and meningoencephalitis. Hepatic involvement is most common and may lead to a fatal outcome. Hematologic abnormalities include eosinophilia and atypical lymphocytosis, and more rarely agranulocytosis and thrombocytopenia [9]. The pathophysiology of AHS has not been fully elucidated although it is thought to be related to an immunologic response. Aromatic anticonvulsants are metabolized by the cytochrome P-450 enzyme to a common arene oxide metabolite, which is normally detoxified by enzymes such as epoxide hydroxylase. Genetically determined abnormalities in enzyme systems, however, may lead to an accumulation of these toxic metabolites, which, in turn, can irreversibly modify cellular proteins, and initiate or serve as targets for an immune attack on modified proteins in target organs [10,11]. An association between active human herpes virus infection and severe AHS has been reported [12,13].

AGEP is clinically characterized by the acute onset of eruptions, numerous small nonfollicular pustules on widespread erythema, high-grade fever, and spontaneous healing within 15 days [14]. Most of the drugs which cause AGEP are antibiotics with β-lactams. To the best of our knowledge, there are only a few reports in the literature of carbamazepine-induced AGEP [1,4,5]. Typical histopathological findings of AGEP are spongiform subcorneal and/or intraepidermal pustules, and perivascular cellular infiltrates [15,16]. As is evident, our patient exhibited typical clinical and pathologic features of AGEP. Differential diagnosis of generalized pustular eruptions in adults should include subcorneal pustular dermatosis, eosinophilic pustular folliculitis, pustular psoriasis, and AGEP, among others. While many studies have shown the usefulness of the lymphocyte transformation test and patch testing in the diagnosis of AGEP, we were unable to perform these due to a lack of patient cooperation.

AHS can be treated by quickly withdrawing the offending drug and administering systemic corticosteroids. Further controlled studies, however, are required to evaluate the efficacy of systemic corticosteroids in AHS [17]. Treatment with high-dose intravenous N-acetylcysteine has also been recently proposed [18]. In conclusion, AHS may present with a nonfollicular pustular eruption rather than the more commonly associated macular papular rash or erythema.

References


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