

# Lymphoma or Pseudolymphoma?

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Anticonvulsant hypersensitivity syndrome is a systemic illness that presents most commonly as a triad of fever, rash, and lymphadenopathy in a patient exposed to one or more of the aromatic antiepileptic drugs (phenytoin, phenobarbital, and carbamazepine). Although generally self-limited, the syndrome may be life-threatening, particularly among patients who develop severe cutaneous eruptions or hepatitis. Early recognition of the syndrome is essential, as immediate discontinuation of the offending antiepileptic agent is the most important step in improving outcome. We present a case of anticonvulsant hypersensitivity syndrome in a patient with a previous history of Hodgkin's lymphoma.

A 35-year-old African-American man with a history of Hodgkin's lymphoma diagnosed in 1983 (treated with chemotherapy) presented in November of 2001 with a 2-week history of an extensive painful pruritic rash. The rash began on his arms and spread to his legs, back and chest. He complained of subjective fever with chills, night sweats, and myalgias. In addition, he reported nontender "swollen lumps" in his neck. He had a history of a traumatic brain

injury secondary to an assault 1 month previously and had been started on phenytoin at a rehabilitation facility for the prophylaxis of seizures. The phenytoin was discontinued 2 days prior to presentation.

His past medical history is significant for a right mastoid fracture 1 month prior to admission (sustained at the time of his assault) and Hodgkin's disease. Past surgical history is significant for a splenectomy for the staging of Hodgkin's disease. He has a 20-pack-year his-

### CME INFORMATION

#### TARGET AUDIENCE

The July/August Clinical Case of the Month is intended for all physicians, especially family physicians, internists, general practitioners, pediatricians, emergency medicine physicians, dermatologists, hematologists-oncologists, clinical pharmacologists, and neurologists, and is also intended for clinical pharmacists.

#### EDUCATIONAL OBJECTIVES

After reading this article, physicians be able to better identify and understand the epidemiology, clinical presentation, pathogenesis, and treatment of the anticonvulsant hypersensitivity syndrome.

#### CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) hour of category 1 credit toward the AMA

Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

#### DISCLOSURE

Dr. Kruspe has nothing to disclose.  
Dr. Broussard has nothing to disclose.  
Dr. Santanilla has nothing to disclose.  
Dr. Gupta has nothing to disclose.  
Dr. Espinoza has nothing to disclose.  
Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.  
Dr. Kantrow has nothing to disclose.

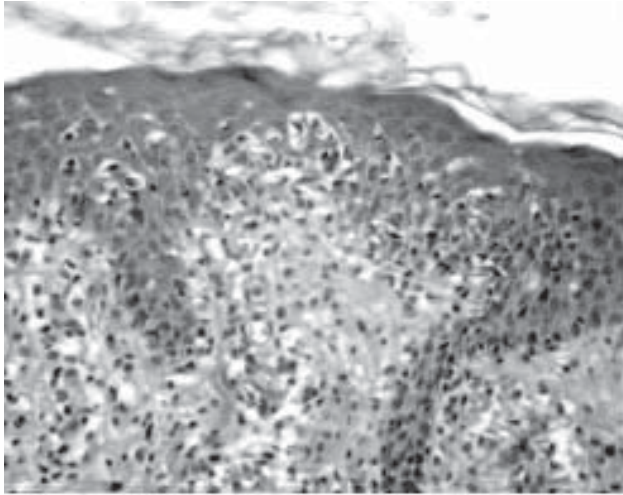
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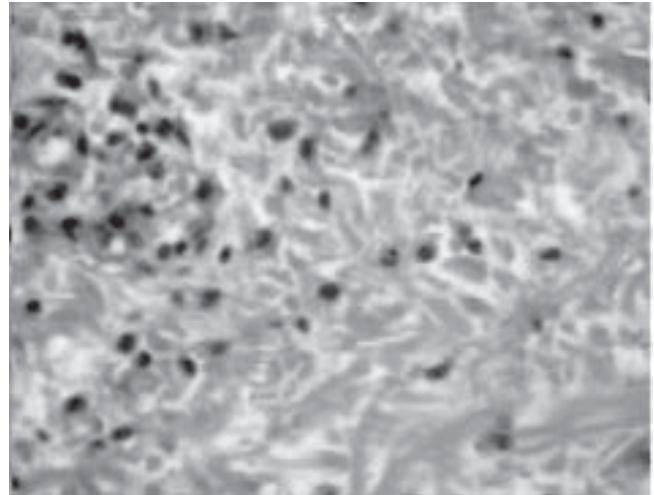


**Figure 1.** Skin, involvement of the lower portion of the epidermis and of the dermis by a moderate inflammatory cell infiltrate composed of lymphocytes, eosinophils and neutrophils. Hematoxylin and Eosin. Original magnification 25X.

tory of tobacco smoking. He has consumed 2 to 3 beers daily for the past 20 years, and he uses marijuana occasionally. He lives with his girlfriend and has a history of "venereal disease" which was treated 15 years ago.

On initial physical examination, he appeared ill. His vital signs were: temperature of 102.1° F, a regular pulse of 130, a blood pressure of 124/66 mmHg, and a respiratory rate of 16 breaths per minute. Cardiovascular examination was significant for tachycardia. Auscultation revealed clear lung fields. Abdominal examination was without abnormalities and extremity examination revealed equal femoral and dorsalis pedis pulses bilaterally. Skin examination revealed a fine nonblanching maculopapular rash with generalized erythema over the entire body. There were bilateral auricular, posterior cervical, right occipital, and submental nodes described as nontender, mobile, and 1 cm in diameter. A complete blood cell count differential revealed a total blood cell count of 11,000  $\mu^3$  with an eosinophilia of 7% and an atypical lymphocytosis of 6%. Transaminases (SGOT/SGPT) were elevated at 83  $\mu$ /L (normal range, < 45  $\mu$ /L) and 81  $\mu$ /L (normal range, < 46  $\mu$ /L) respectively with an alkaline phosphatase of 163  $\mu$ /Liter (normal range, 20-120  $\mu$ /L). Urinalysis was remarkable for moderate blood with 26-50 rbc/hpf. Human Immunodeficiency Virus, rapid plasma reagin, and monospot tests were negative.

The differential diagnosis at admission included possible anticonvulsant hypersensitivity syndrome, rash of infectious etiology, or lymphoproliferative disorder. The patient was given oral prednisone and intravenous gatifloxacin, and a skin biopsy was performed. On hospital day 2, he developed periorbital edema. On hospi-



**Figure 2.** Skin, detail of dermal inflammatory cell infiltrate. Notice extravasated erythrocytes and eosinophils. Hematoxylin and Eosin. Original magnification 50X.

tal day 3, he continued to have elevated temperatures, and intravenous solumedrol was started, in lieu of prednisone. By hospital day 5, he was afebrile and his rash had markedly improved. Blood cultures revealed no growth and the gatifloxacin was discontinued. The skin biopsy revealed changes consistent with hypersensitivity reaction (Figure 1). On hospital day 7, he was discharged to home on a prednisone taper.

### ANTICONVULSANT HYPERSENSITIVITY SYNDROME

Anticonvulsant hypersensitivity syndrome (AHS) refers to the constellation of cutaneous and systemic reactions associated with the aromatic antiepileptic drugs (ie, phenytoin, phenobarbital and carbamazepine). This syndrome is most commonly characterized by fever, rash and lymphadenopathy, but may also be accompanied by hepatitis, facial edema, pharyngitis, arthralgias, nephritis, and hematologic abnormalities. Although once referred to as phenytoin hypersensitivity reaction, the syndrome has been appropriately renamed to reflect its association with each of the arene oxide-producing anticonvulsants. Gingival hyperplasia, another well-known adverse effect of phenytoin, appears unrelated to the development of anticonvulsant hypersensitivity.

#### Incidence

While the exact incidence of AHS remains uncertain, the overall risk of developing the syndrome is approximately 1/1,000 to 1/10,000.<sup>1</sup> Two patient populations have been identified as being at greatest risk. The first

group consists of those who have had a prior reaction to an aromatic anticonvulsant and are re-exposed to the same or another drug in the class.<sup>2</sup> A second high risk population includes the first-order relatives of patients with a history of AHS. Findings from *in vitro* studies suggest that the syndrome may follow an autosomal codominant pattern of inheritance.<sup>3</sup> AHS seems to show no age or gender predisposition; however, reviews of the literature have suggested an association with African-American patients. While the majority of reported cases have occurred in African-American patients, it remains unclear whether this phenomenon represents a genuine racial predilection or simply selection or reporting bias.

### Onset

When compared to other causes of drug-induced hypersensitivity, AHS typically exhibits a more delayed onset.<sup>4</sup> The syndrome generally occurs within the first 3 months of treatment, with most reactions occurring 2 to 6 weeks after initiation of therapy. However, sensitized patients with a history of AHS may present within 1 day of resuming therapy with an aromatic anticonvulsant. A high spiking fever (38° to 40°C) is often the first clue of impending AHS, usually preceding the appearance of cutaneous findings by several days.<sup>5</sup> Once the anticonvulsant has been discontinued, these temperature spikes resolve slowly over the course of several weeks.

### Cutaneous Features

Along with fever and lymphadenopathy, the most common dermatologic manifestation is a morbilliform rash (measles-like). The rash is one of the hallmarks of anticonvulsant hypersensitivity. While specific cutaneous findings may vary among patients, a frequently observed pattern has been described.<sup>5</sup> The rash usually appears first on the arms, face, and upper trunk as a patchy, erythematous macular eruption. With progression of the syndrome, prominent periorbital and facial edema may emerge, and inflammation of the conjunctiva and pharynx becomes marked. Eventually, the lower extremities become involved as the affected areas become pruritic and develop a confluent, papular appearance. Less frequently, the eruption may then become pustular or a generalized desquamative erythroderma. Histologic examination of these pustules demonstrates a dense, perivascular lymphocytic infiltrate with a variable degree of edema (Figure 2).<sup>2</sup> Other cutaneous manifestations seen more rarely include erythema multiforme (from mild forms to Stevens-Johnson syndrome and toxic epidermal necrolysis), exfoliative, bullous, purpuric, and urticarial dermatitis. Although rare, the severe forms of erythema multiforme may follow re-exposure in an individual with a prior hypersensitivity reaction to one of the aromatic anticonvulsants.

### Extracutaneous Features

Following fever and rash, lymphadenopathy is the third most common manifestation of AHS. Enlarged lymph nodes may be localized or generalized and are usually tender. Biopsy of these nodes most often reveals benign lymphoid hyperplasia; however, malignant-appearing pseudolymphomatous changes (ie, focal necrosis and destruction of normal lymph node architecture) have been described.<sup>6</sup> Classically, both the benign and seemingly malignant changes slowly resolve after discontinuation of the anticonvulsant drug. However, there have been several case reports of "pseudopseudolymphoma," or truly malignant lymphoma, associated with anticonvulsant use.

As a feature of AHS, hepatitis is generally anicteric and is most often characterized by enlargement of the liver and a significant rise in aminotransferase levels.<sup>2</sup> Toxicity is primarily due to damage of the hepatocytes with resultant necrosis, although injury to the bile ducts may also occur. Patients with hepatitis secondary to AHS must be closely monitored because the mortality rate ranges from 10% to 50%. Prompt recognition of the cause of hepatitis is essential. Liver failure is the most frequent cause of death in patients with AHS, and the degree of hepatitis is proportionally related to the period between symptom onset and discontinuation of the offending drug.<sup>5</sup> Resolution usually takes several months and may even require a year or longer.

Hematologic abnormalities are also frequently associated with hypersensitivity to the aromatic anticonvulsants. Common findings include leukocytosis, eosinophilia, and the presence of atypical lymphocytes.<sup>7</sup> An absolute eosinophil count greater than  $1.5 \times 10^3/\mu\text{L}$  is inherently toxic to endothelial cells and has been associated with damage to the heart, gastrointestinal tract, lungs, and kidneys in patients with AHS.<sup>5</sup> A Coombs' negative hemolytic anemia has also been described.

Other systemic manifestations of AHS reported in the literature include arthralgias, myopathy and subsequent rhabdomyolysis, and interstitial nephritis with occasional progression to renal failure.<sup>8,9</sup>

### Etiology

Researchers have yet to uncover the specific mechanisms involved in the anticonvulsant hypersensitivity syndrome. The syndrome is probably linked to the cytochrome P450-mediated production of intermediate metabolites known as arene oxides.<sup>10</sup> In patients without AHS, these metabolites are detoxified by epoxide hydroxylase before any deleterious effects may occur. Conversely, many patients who develop hypersensitivity to aromatic anticonvulsants may be unable to detoxify arene oxide compounds due to absent or defective epoxide hydroxylase. These arene oxide metabo-

lites then build up within cells and produce toxic effects after binding to cellular macromolecules, possibly by direct cytotoxicity or perhaps by acting as immunogens to initiate a systemic immunologic response.<sup>11</sup> Abnormal detoxification of arene oxide compounds appears to be inherited as an autosomal codominant trait. While widely available *in vitro* testing for this trait is not yet available, it may be of future use to first-order relatives of individuals with a history of AHS.

## Treatment

Other than prompt termination of the responsible drug, there is no specific treatment for AHS.<sup>7</sup> Timely diagnosis of the syndrome is crucial as severity is related in part to the length of time between symptom onset and discontinuation of the anticonvulsant. A careful drug history must be elicited from any patient who presents with fever, a generalized maculopapular rash, lymphadenopathy, hepatitis, and leukocytosis with eosinophilia.

Treatment is primarily supportive and is directed at maintaining nutrition and fluid and electrolyte status.<sup>5</sup> Hematologic, hepatic, and renal function should be followed closely with serial CBCs, liver function studies, and serum blood urea nitrogen and creatinine levels. Antihistamines and topical corticosteroids may provide symptomatic relief of cutaneous inflammation and pruritis. As in our patient, systemic corticosteroids (=0.5 mg/kg) may also be used, often resulting in significant symptomatic improvement.<sup>4</sup> No randomized, placebo-controlled, clinical trials, however, have examined the issue of systemic steroids in AHS, so their precise role remains undefined. Despite occasional relapses of rash and hepatitis, complete resolution over a period of weeks to months (and, in some cases, years) occurs in a majority of patients.

Patients with AHS who require an antiepileptic drug for control of a seizure disorder should not be treated with any of the aromatic anticonvulsants (phenytoin, carbamazepine and phenobarbital).<sup>5</sup> During the acute and convalescent phases of the hypersensitivity syndrome, seizure control is best achieved with a benzodiazepine. Once the patient has recovered more fully, valproic acid is an alternative anti-epileptic. However, valproic acid should be avoided until the AHS-associated hepatitis has resolved because it is metabolized by the liver. Newer anticonvulsants such as gabapentin and lamotrigine also show promise as alternative therapies in patients with a history of hypersensitivity to the aromatic antiepileptic drugs.

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## CME QUESTIONS

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**For each question, choose the one answer that is most correct.**

1. The anticonvulsant hypersensitivity syndrome (AHS) refers to a constellation of findings which may include:
  - a) rash
  - b) fever
  - c) lymphadenopathy
  - d) hematologic abnormalities
  - e) all of the above
2. True or False: Patients with a prior history of hypersensitivity to anticonvulsants and first-order relatives of patients with a history of anticonvulsant hypersensitivity syndrome are the two groups at greatest risk for AHS.

3. True or False: Most patients will develop anticonvulsant hypersensitivity syndrome within minutes of receiving an aromatic aromatic antiepileptic drug.
4. Hematologic abnormalities commonly associated with AHS include all of the following except:
  - a) leukocytosis
  - b) atypical lymphocytes
  - c) elevated hemoglobin
  - d) eosinophilia
5. Anticonvulsants commonly associated with AHS include all of the following except:
  - a) phenytoin
  - b) carbamazepine
  - c) valproic acid
  - d) phenobarbital
6. True or False: The most common cutaneous manifestation of AHS is erythema multiforme.
7. True or False: *In vitro* testing to diagnose for abnormal detoxification of arene oxide compounds is widely available and is recommended for all patients beginning an antiepileptic agent.
8. Treatment of AHS includes all of the following except:
  - a) prompt termination of the anticonvulsant
  - b) supportive care with close attention to nutrition, fluid, and electrolyte status
  - c) serial measurements of renal, hematologic and liver function
  - d) use of another aromatic anticonvulsant
  - e) symptomatic relief of pruritus with topical corticosteroids or antihistamines
9. True or False: The anticonvulsant hypersensitivity syndrome is generally self-limited with complete resolution occurring in the majority of patients.



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