INTERNAL MEDICINE

□ CASE REPORT □

Late-onset Anticonvulsant Hypersensitivity Syndrome Mimicking Lymphoma

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Abstract

Anticonvulsant hypersensitivity syndrome is a fatal, idiosyncratic drug reaction that is caused by aromatic antiepileptic drugs. This cutaneous drug reaction is also called pseudolymphoma because of its clinical and histological similarities with malignant lymphoma. The primary clinical findings are fever, skin rashes, enlarged lymph nodes, single or multiple internal organ involvement and hematological abnormalities. Typically, anticonvulsant hypersensitivity syndrome occurs 1-8 weeks after drug administration. We herein present the case of a patient who had been on anticonvulsant therapy for five years and died from late-onset anticonvulsant hypersensitivity syndrome.

Key words: anticonvulsant hypersensitivity syndrome, lymphadenopathy, pseudolymphoma

(Intern Med 54: 3201-3204, 2015)
(DOI: 10.2169/internalmedicine.54.5111)

Introduction

Anticonvulsant hypersensitivity syndrome (AHS) is a specific type of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. AHS is a life-threatening, idiosyncratic drug reaction that is associated with aromatic antiepileptic drugs, such as carbamazepine, phenobarbital and phenytoin, as well as new-generation drugs, such as lamotrigine. Its pathophysiology is not understood completely, although a genetic predisposition related to certain enzyme deficits, lymphocyte activation, herpes virus activation and specific human leukocyte antigen (HLA) alleles might be responsible for its pathogenesis (1). This cutaneous drug reaction is also called pseudolymphoma because of its clinical and histological similarities with malignant lymphoma (2). The primary clinical findings are fever, skin rashes, enlarged lymph nodes, single or multiple internal organ involvement and hematological abnormalities, such as atypical lymphocytosis and eosinophilia. Typically, AHS occurs 1-8 weeks after drug administration. Its incidence is 1/1,000 to 10,000 exposures with a mortality rate of 10-20% (3). This report presents the case of a patient who was diagnosed with valproic acid-induced aplastic anemia at 16 years of age and died from late-onset anticonvulsant hypersensitivity syndrome at 32 years of age.

Case Report

A 32-year-old woman was admitted to our hematology department four months after being diagnosed with normocytic normochromic anemia. She reported a 3-week history of general weakness, fever, and cough. She had undergone surgery and radiotherapy for a cerebellar cyst at 3 years of age and had been diagnosed with epilepsy at 10 years of age, after which she was treated with sodium valproate. At 16 years of age, her treatment was changed to clonazepam due to valproic acid-induced aplastic anemia. At the time of admission to our hospital, she had been taking lamotrigine, clonazepam and topiramate for five years because of recurrent epileptic seizures.

On a physical examination, the patient had pale skin, facial edema and a fever (38℃). Upon auscultation of the lungs, crepitant rales were heard basally bilaterally, more prominently on the right. Bilateral axillary and inguinal lymphadenopathy (LAP) was noted; the nodes were approxi-

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Received for publication February 9, 2015; Accepted for publication April 12, 2015
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Table 1. Laboratory Test Results.

WBC	7.45	×10³/μL	(4.6-10.2)	d.Coombs	1+		
Neu	5.68	×10³/μL	(2.0-6.9)	Haptoglobulin	71	mg/dL	(30-200)
Lym	1.60	×10³/μL	(0.6-3.4)	ESR	10	mm/h	(<20)
Eos	0.01	×10³/μL	(0.0-0.7)	CRP	16	mg/dL	(0-0.5)
Hg	7.4	g/dL	(12.2-18.1)	HBsAg	0.21	S/CO	(<1.0-N)
Hct	22	%	(37.7-53.7)	AntiHBs	>1,000	IU/L	(>10-P)
MCV	99.8	fL	(80-97)	AntiHCV	0.11	S/CO	(<1.0-N)
PLT	215	×10³/μL	(142-424)	AntiHIV	0.22	S/CO	(<1.0-N)
Rtc	1.17	%	(0.39-7.54)	EBV IgM	Negative		
Urea	39	mg/dL	(15-55)	CMV IgM	Negative		
Cre	1.02	mg/dL	(0.6-1.3)	RoseBengal	Negative		
AST	20	U/L	(5-34)	Gruber-Widal	Negative		
ALT	6	U/L	(0-55)	ANA	Hom 2+/granular 4+		
T.bil	0.3	mg/dL	(0.2-0.8)	Anti dsDNA	Negative		
LDH	246	U/L	(125-245)	Anti-histone	1+		
Alb	2.52	g/dL	(3.5-5)	Blood culture	Negative		
Glo	5.98	g/dL	(1.1-3.5)	Urine culture	Negative		
B12	193	pg/mL	(126-505)	Stool culture	Negative		
Folic acid	2.7	ng/mL	(3.1-19.9)	SIE*	Polyclonal hypergammaglobulinemia		
Ferritin	194	ng/mL	(11-306)				

*Serum Immunofixation Electrophoresis

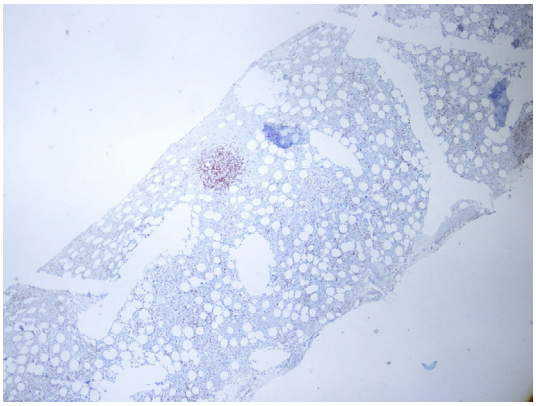


Figure 1. CD3-stained specimens of bone marrow revealed T lymphocytic nodules. ×40.

mately 2 cm in diameter. The spleen was palpable 2 cm below the left costal margin. Laboratory tests revealed normocytic normochromic anemia, increased acute phase reactants and folate deficiency (Table 1). Folic acid and empirical levofloxacin (500 mg a day) treatment was thus initiated. Lymphoma and aplastic anemia were considered in the differential diagnosis, and a bone marrow biopsy and excisional lymph node biopsy of the inguinal area were performed. Thorax and abdomen computed tomography (CT) revealed consolidation in the lower lobes of both lungs (prominent on the right), peribronchial thickening, marked pericardial and pleural effusion, an enlarged spleen (15 cm), bilateral iliac chain, inguinal, paratracheal and subcarinal LAP approximately 2 cm in diameter and small amounts of free fluid in the pelvis. The patient refused bronchoscopy and thoracentesis.

Antinuclear antibody (ANA) and anti-histone tests were positive. Therfore the patient was referred to the rheumatology department, and oral methylprednisolone (1 mg/kg/day) was added to her treatment regimen for suspected drug-induced lupus erythematosus (DILE). Upon consulting the neurology department, lamotrigine was stopped and the doses of the other anti-epileptics were reduced. Three weeks later, she presented with dyspnea and generalized edema with increased liver enzyme [aspartate aminotransferase (AST) 220 U/L, alanine aminotransferase (ALT) 345 U/L] and creatinine (2.5 mg/dL) levels. On a bone marrow biopsy, the cellularity was 60%, with four interstitial reactive lymphoid nodules that showed positive staining for CD3 and CD7, as well as marked interstitial mature plasmacytosis, CD3+ lymphocytosis and eosinophilia (Fig. 1). Monoclonal kappa/lambda light chain, CD10, FMC7 and PD-1 were detected negative on a flow cytometric analysis of bone marrow aspirate. A conventional cytogenetic analysis revealed the 46 XX diploid karyotype in 24 metaphases. Additionally t(11:14)(q13;32), t(14:18)(q32;21), t(8:14)(q24;32), del 17p13.3 and IgH gene rearrangement was detected at findings of %100 negative on *in situ* hybridization. An excisional LAP biopsy revealed polymorphic infiltration composed of immunoblasts, lymphocytes, plasma cells and eosinophils with a protected architecture in the lymph node. There were no signs of hyalinization, storiform fibrosis, obliterative phlebitis, perinodal infiltration or marked proliferation of high endothelial venules and/or interfollicular vessels. Immunohistochemically, the majority of infiltration involved kappa/lambda polyclonal CD38+ plasma cells. T cells showed a CD3 +, CD7 +, CD10 - and bcl-6 negative staining pattern (Fig. 2). Both biopsy results were reported as showing anticonvulsant hypersensitivity syndrome. The patient developed muscle weakness followed by respiratory, cardiac, liver and renal failure and was transferred to the intensive care unit. All anticonvulsant drugs were stopped, and treatment with intravenous (IV) methylprednisolone (1 g/day) for three days and IV immunoglobulin (1 g/kg/day) for five days was initiated. Unfortunately, there were no signs of clinical improvement, and the patient underwent five courses of plasmapheresis. However she did not respond to

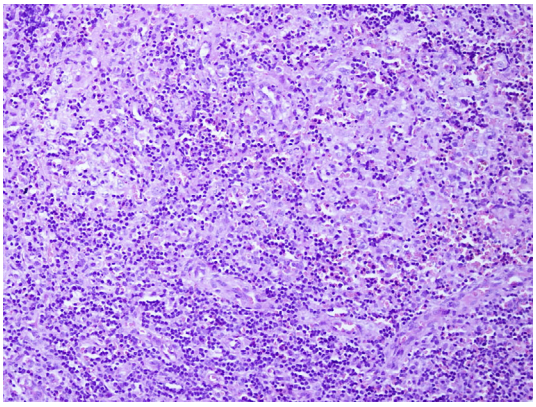


Figure 2. Hematoxylin and Eosin staining specimens of a lymph node revealed the infiltration of eosinophils. ×200.

treatment and died of multi-organ failure.

Discussion

The exact mechanism of DRESS remains to be determined; however in cases related to anticonvulsant drugs, three factors may be considered: deficient or abnormal epoxide hydroxylase, the enzyme that detoxifies the metabolites of aromatic amine anticonvulsants (metabolic pathway); associated sequential reactivation of the herpesvirus family; and ethnic predisposition with certain HLA alleles (immune response) (4). The HLA alleles most commonly reported in patients with DRESS syndrome are HLA-B*57:01, HLA-B*15:02 and HLA-A*31:01.

The activation of chronic persistent viruses of the human herpes virus (HHV) family, including HHV-6/7, cytomegalovirus (CMV) and Epstein-Barr virus (EBV), has been described in association with most, but not all, drugs implicated in DRESS syndrome. The HHV most commonly reported to be reactivated is HHV-6. More recently, HHV-7, EBV and CMV reactivation has also been observed in up to 76% of patients with DRESS syndrome (5). In the current case, serology for EBV, CMV and hepatitis B and C viruses was negative and no seroconversion was observed at follow-up. Although HHV-6 reactivation is the most common triggering factor in DRESS syndrome, we were unable to study HHV-6 for technical reasons.

Skin lesions are observed in 90% of affected patients, including facial edema, erythema multiforme, Stevens-Johnson syndrome, common morbilliform lesions, erythroderma and oral lesions (1). The most commonly involved internal organ is the liver, associated with hepatitis, although nephritis, pneumonitis and pancreatitis can also occur.

Confirming the diagnosis of AHS can be difficult because of the variety of clinical features and laboratory abnormalities, and there is no reliable standard for diagnosing anticonvulsant hypersensitivity syndrome. Clinicians must exclude other potentially serious conditions, including infections, malignant processes, autoimmune disorders, and connective tissue disease. The diagnosis is based on clinical and laboratory findings (Table 2), which are helpful, but not always specific. The results of histological examinations of visceral involvement can be nonspecific, although the damaged tissue often contains the accumulation of eosinophils. Lymph nodes are frequently affected in cases of AHS, with the histopathology falling into one of two distinct patterns: benign lymphoid hyperplasia, in which the lymph node architecture is preserved, and pseudolymphoma, with disruption of the normal architecture by a polymorphous infiltrate consisting of atypical cells with mitotic figures, plasma cells, histiocytes and eosinophils, associated with areas of necrosis and edema. There are no Reed-Sternberg cells or capsular invasion. This pseudolymphoma pattern can be difficult to distinguish from that of a true lymphoma (6). Nevertheless, multicentric Castleman disease (MCD), IgG4-related diseases (IgG4-RD) and DILE share many clinical and laboratory findings with DRESS syndrome. IgG4-RD are seen mostly in middle-aged and elderly men. It can affect almost any organ, although the most commonly involved internal organ is the pancreas, with pancreatitis. In addition hepatobiliary tract, salivary gland, orbit and lymph node involvement can be seen. In cases of IgG4-RD, dense lymphoplasmacytic infiltrates, storiform fibrosis and obliterative phlebitis are commonly observed on biopsies (7). Since neither storiform fibrosis nor obliterative phlebitis were detected in the lymph node biopsy of our patient, we excluded IgG4-RD in this case. MCD is a systemic disease that commonly occurs in the setting of HIV infection and is characterized by diffuse lymphadenopathy, splenomegaly, anemia and systemic inflammatory symptoms (8). Increased IL-6 levels can be seen in both MCD and AHS. In the current case, the histopathological findings revealed no signs of hyalinization, marked proliferation of interfollicular vessels or hyperplastic follicles, which are frequently seen in MCD. Although aplastic anemia, lymphoma [especially angioimmunoblastic T cell lymphoma (AITL)] and DILE were also considered in the differential diagnosis in the present case, we excluded these diagnoses during follow-up and according to the results of various tests. In patients with AITL, immunohistochemical staining is positive for CD10, BCL-6 and PD-1, although this was found to be negative in our patient (9). T cell receptor (TCR) gene rearrangement is considered to be a good supplementary method for differentiating AHS from AITL; however, we were unable to study TCR gene rearrangement for technical reasons.

The treatment of DRESS syndrome is based on early recognition and withdrawal of the offending drug. There have been no successful controlled trials of AHS treatment. In addition, systemic steroid use remains controversial, and there are no sufficient studies on this subject. However, this treatment is recommended for patients with internal organ involvement. Regarding IV immunoglobulin use, there is no consensus in terms of dosage, which varies greatly. Previous patients have been given 1-4 days of therapy at doses of 0.5 mg/kg/day or 2 g/kg/day and all subjects who received intravenous immunoglobulin (IVIG) have benefited from it (10, 11). Although there are reports of the use of N-

Table 2. Diagnostic Criteria for Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome.

Bocquet et al.[15]	RegiSCAR	J-SCAR*
Cutaneous drug eruption	Acute rash†	Maculo papular rash developing>3 weeks after starting offending drug
Hematologic abnormalities	Reacttion suspected to be drug-related†	
Eosinophils≥1.5×10^9/L	Hospitalization†	Prolonged clinical symptoms after discontinuation of the causative drug
Presence of atypical lymphocytes	Fever >38˚C‡	Fever >38ºC
	Enlarged lymph nodes involving	Liver abnormalittes (ALT>100 U/L) or
Systemic involvement	≥2 sıtes‡	other organ involvement
Adenopathy:lymph nodes≥2 cm in diameter	Involvement of ≥1 internal organ‡	
		Leukocyte abnormalities (≥ 1)
Hepatitis with liver	Blood count abnormalities‡	Leukocytosis (>11 × 10^9 /L)
transaminases ≥ 2 times normal	Lymphocytes above or below normal	Atypical lymphocytes (>5%)
Interstitial nephritis	limits	Eosinophilia (>1.5 × 10^9 /L)
Interstitial pneumonitis	Eosinophils over laboratory limits	
Carditis	Platelets under laboratory limits	Lymphadenopathy
		HHV-6 reactivation

For Bocquet et al. criteria all 3 criteria are required (1 hematologic and 1 systemic feature required).
DIHS: Drug-induced hypersensitivity syndrome, HHV-6: human herpes virus-6, J-SCAR: Japanese Research Committee on Severe Cutaneous Adverse Reaction, RegiSCAR: European Registry of Severe Cutaneous Adverse Reaction
*J-SCAR criteria includes DIHS. Typical DIHS is defined as the presence of all 7 criteria, while atypical DIHS is defined as the presence of all 7 criteria, while atypical DIHS is defined as the presence of the first 5 criteria only.
†Necessary criteria for diagnosis according to RegiSCAR.
‡Three of these 4 criteria reguired for diagnosis according to RegiSCAR.
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acetylcysteine, pentoxifylline, levamisole, and plasmapheresis in the treatment of AHS, there are no well-controlled, prospective clinical trials (12). The mortality rate of AHS is approximately 10% (6). Secondary bacterial infections and organ failure are the most common causes of mortality, and the mortality risk is increased in patients with a high eosinophil count and multiple organ involvement associated with an underlying chronic disease (13).

To our knowledge, this is the second reported case of anticonvulsant hypersensitivity syndrome occurring during long-term treatment. Rodríguez et al. reported a case treated with phenytoin, lamotrigine and clobazam for seven years in which the patient presented with hepatic and renal failure in relation to AHS demonstrated on a renal biopsy (14). These cases indicate that anticonvulsant hypersensitivity syndrome should be kept in mind at all stages of treatment for epilepsy. The offending drugs should be discontinued immediately, and treatment should be continued with drugs from different groups; multiple organ failure can develop if treatment is delayed. Notably, the present patient died of multiple organ failure. Hence, clinicians should be aware of this clinical condition, which can be fatal.

The authors state that they have no Conflict of Interest (COI).

References

1. Hautmann G, Lotti T. Psychoactive drugs and skin. J Eur Acad Dermatol Venereol **17**: 383-393, 2003.
2. Saltzstein SL, Ackerman LV. Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically pathologically malignant lymphomas. Cancer **12**: 164-182, 1959.
3. López-Rocha E, Blancas L, Rodríguez-Mireles K, et al. Prevalance of DRESS Syndrome. Rev Alerg Mex **61**: 14-23, 2014.
4. Criado PR, Criado RF, Avancini JM, Santi CG. Drug reaction with Eosinophilia and Systemic Symptoms (DRESS)/Drug-induced Hypersensitivity Syndrome (DIHS): a review of current concepts. An Bras Dermatol **87**: 435-449, 2012.
5. Pavlos R, Mallal S, Ostrov D, Pompeu Y, Phillips E. Fever, rash, and systemic symptoms: understanding the role of virus and HLA in severe cutaneous drug allergy. J Allergy Clin Immunol Pract **2**: 21-33, 2014.
6. Husain Z, Reddy B, Schwartz R. DRESS Syndrome. J Am Acad Dermatol **68**: 693.e1-e14; quiz 706-708, 2013.
7. Guma M, Firestein GS. IgG4-related diseases. Best Pract Res Clin Rheumatol **26**: 425-438, 2012.
8. Soumerai JD, Sohani AR, Abramson JS. Diagnosis and management of castleman disease. Cancer Control **21**: 266-278, 2015.
9. Dogan A, Attygalle AD, Kyriakou C. Angioimmunoblastic T-cell lymphoma. Br J Haematol **121**: 681-691, 2003.
10. Prais D, Straussberg R, Amir J, Nussinovitch M, Harel L. Treatment of anticonvulsant hypersensitivity syndrome with intravenous immunoglobulins and corticosteroids. J Child Neurol **21**: 380-384, 2006.
11. Santos RP, Ramillo O, Barton T. Nevirapine-associated rash with eosinophilia and systemic symptoms in a child with human immunodeficiency Virus Infection. Pediatr Infect Dis J **26**: 1053-1056, 2007.
12. Sahin E, Karaman G, Şendur N, Savk E. Four cases of anticonvulsant hypersensitivity syndrome. Adnan Menderes Üniversitesi Tıp Fakültesi Dergisi (Journal of Adnan Menderes University Medical Faculty) **7**: 39-42, 2006 (in Turkish, Abstract in English).
13. Yılmaz EA, Ozmen S, Tuygun N, Ginis T, Tanir G. Lamotrigine associated dress syndrome: a case report. Çocuk Dergisi (The Journal of the Child) **9**: 142-146, 2009 (in Turkish, Abstract in English).
14. Rodríguez-Osorio X, Pardo J, López-González FJ, Novoa D, Pintos E. Levetiracetam following liver and kidney failure in late-onset anticonvulsant hypersensitivity syndrome. J Clin Neurosci **21**: 859-860, 2014.
15. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). Semin Cutan Med Surg **15**: 250-257, 1996.

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