

Differentiation of angioimmunoblastic T-cell lymphoma from DRESS syndrome



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Clinical Implications

- Angioimmunoblastic T-cell lymphoma masquerading as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome may be differentiated from true DRESS syndrome based on low drug causality probability, less hepatic involvement, and lymphoma-specific involvement of lymph nodes and spleen. Early lymph node biopsy should be performed.

TO THE EDITOR:

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a form of severe systemic drug reaction characterized by fever, skin rash, eosinophilia, lymphadenopathy, and internal organ involvement. It is also termed anticonvulsant hypersensitivity syndrome, drug-induced delayed multiorgan hypersensitivity syndrome, and drug-induced hypersensitivity syndrome. This clinical picture has also been observed in other diseases, such as viral infection and autoimmune disease. Particularly, a DRESS syndrome—like illness accompanied by lymphadenopathy needs to be differentiated from malignant lymphoma.

Angioimmunoblastic T-cell lymphoma (AITL) is a rare disease that accounts for 1.2% and 18% of non-Hodgkin's and T-cell lymphoma, respectively. Interestingly, patients with AITL may show fever, rash, eosinophilia, and hepatosplenomegaly as well as lymphadenopathy. Rash occurs after drug administration in some patients.¹ A patient has been reported who was initially diagnosed with DRESS syndrome followed by an eventual AITL diagnosis.² It may be crucial to differentiate AITL from suspected DRESS syndrome with lymphadenopathy as soon as possible because the 5-year survival rate of AITL is 30% and median survival time is 1.7 years.³ However, differential features between the 2 diseases have not been studied, possibly because DRESS syndrome—mimicking AITL is very rare. We diagnosed 5 patients with DRESS syndrome—mimicking AITL; thus we aimed to describe clinical and laboratory differences between AITL and DRESS syndrome with lymphadenopathy.

Seventeen patients with lymphadenopathy accompanying DRESS syndrome were recruited among the subjects who had been reported to the Regional Pharmacovigilance Center of Chonnam National University Hospital from January 2011 to December 2016. The inclusion criteria included a European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score ≥ 4 points⁴ and presence of neck, chest, and/or abdominal lymphadenopathy on computed tomography (CT) (see [Figure E1](#) in this article's Online Repository at

www.jaci-inpractice.org). The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality categories⁵ and the Naranjo Adverse Drug Reaction Probability Scale⁶ were used to assess the relationship between suspicious drug and DRESS syndrome.

Five patients were diagnosed with AITL by cervical lymph node biopsy and T-cell receptor (TCR) gene rearrangement, although they were initially suspected of having DRESS syndrome. The biopsy specimens were stained with hematoxylin-eosin and for CD3, CD20, CD21, and Epstein-Barr virus. TCR gene rearrangement was performed as described elsewhere.⁷ If either one of the TCRs was detected, positive TCR clonality was considered. CT findings of the lymph nodes, liver, and spleen were also analyzed. This study was approved by the Institutional Review Board at Chonnam National University Hospital.

Individual characteristics of patients with AITL are described in [Table I](#). All showed TCR- β and/or TCR- γ clonality, 1 (case 4) received chemotherapy, and all died because of septic complications. All 5 cases with AITL showed maculopapular exanthem. The median age of the 17 patients with DRESS syndrome was 51 years (range, 15-83 years); the DRESS syndrome group included 8 women. The median RegiSCAR score was 5 (range, 4-7). The following were the causative drugs: carbamazepine, 6 cases; dapsone, 6; allopurinol, 3; lamotrigine, 1; and sulfasalazine, 1. The median Naranjo score was 6 (range, 5-8). According to the WHO-UMC classification, 2 and 15 cases were categorized as "certain" and "probable," respectively. The median latent period was 24 days (range, 4-135 days). The median body temperature was 38.8°C (range, 36.6°C to 39.9°C). There were 14 cases with maculopapular exanthem, 2 with bullous skin reactions, and 1 with desquamative erythroderma. All patients received systemic steroids after quitting the causative drug, resulting in complete recovery.

Clinical and laboratory characteristics of patients with AITL were compared with those of patients with DRESS syndrome. Patients with AITL were older than patients with DRESS syndrome; however, no difference in gender or RegiSCAR scores was observed. Naranjo scores and latent period were lower and shorter, respectively, in AITL than in DRESS syndrome ([Table II](#)). No differences in body temperature were found. C-reactive protein, erythrocyte sedimentation rate, leukocyte, lymphocyte, eosinophil, atypical lymphocyte, hemoglobin, platelet, lactate dehydrogenase, β_2 -microglobulin, and ferritin were not different. Hepatic enzymes were lower and creatinine was higher in AITL ([Table II](#)).

Next, CT findings were compared. Maximal width of chest lymph nodes was higher and patients with ≥ 10 abnormal lymph nodes in the chest, neck, and abdomen were more common in the AITL group than in the DRESS syndrome group. The frequency of hepatomegaly did not differ. Splenomegaly was more frequent in patients with AITL than in patients with DRESS syndrome (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org).

Our results showed that DRESS syndrome—mimicking AITL showed lower drug causality probability, lesser hepatic dysfunction, more big-sized lymphadenopathy, and more frequent splenomegaly than true DRESS syndrome. If cases of suspected

TABLE I. Characteristics of the 5 patients with angioimmunoblastic T-cell lymphoma

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (y)	81	71	70	57	69
Sex	Male	Female	Male	Male	Male
RegiSCAR score	5	4	4	5	6
Suspected drug	Ceftizoxime	Levofloxacin	Cefaclor	Gemifloxacin	Pneumo-23
Naranjo score	2	2	2	2	1
WHO-UMC category	Possible	Possible	Possible	Possible	Possible
Latent period (d)*	12	3	5	5	3
Body temperature (°C)	40.0	38.4	40.0	39.0	39.4
Blood eosinophils, % (/μL)	30.6 (4200)	0.9 (80)	4.3 (1300)	38.9 (6400)	17.7 (3910)
Atypical lymphocytes (%)	7	0	0	1	8
Lymphadenopathy	Neck on palpation	Neck on CT	Neck, chest, and abdomen on CT	Neck and chest on CT	Neck, chest, and abdomen on CT
AST (U/L)	19	58	62	30	37
ALT (U/L)	16	18	68	27	93
Creatinine (mg/dL)	1.3	1.6	0.7	1.4	1.4
Survival time (d)†	542	12	19	244	16

ALT, Alanine transaminase; AST, aspartate transaminase; CT, computed tomography; DRESS, drug reaction with eosinophilia and systemic symptoms; RegiSCAR, European registry of severe cutaneous adverse reactions; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

*Interval from the first day of drug administration to onset of DRESS syndrome-like manifestation.

†Period from onset of DRESS syndrome-like manifestation to death.

TABLE II. Comparison of clinical and laboratory data between angioimmunoblastic T-cell lymphoma and DRESS syndrome cases

Data	Angioimmunoblastic T-cell lymphoma (n = 5)	DRESS syndrome (n = 17)
Naranjo score*	2 (1-2)	6 (5-8)
Latent period (d)†	5 (3-12)	24 (4-135)
CRP (mg/dL)	6.5 (0.7-19.1)	5.4 (0.1-16.6)
ESR (mm/h)	19.5 (2-34)	15.5 (2-52) (n = 16)
Leukocytes (×10 ³ /μL)	16.5 (9-22.1)	14.3 (5.1-44.6)
Lymphocytes (×10 ³ /μL)	2.5 (1-6.1)	4.2 (0.6-24.5)
Eosinophils (×10 ³ /μL)	3.9 (0.08-6.4)	0.7 (0-5.2)
Atypical lymphocytes (%)	1 (0-8)	2 (0-34)
Hemoglobin (g/dL)	11.6 (10.0-13.8)	11.7 (10.0-14.4)
Platelets (×10 ³ /μL)	103 (54-332)	188 (84-327)
AST (U/L)	37 (19-62)	100 (21-470)
ALT (U/L)	27 (16-93)	183 (6-670)
Total bilirubin (mg/dL)	1.6 (0.6-1.8)	0.8 (0.5-10.0)
BUN (mg/dL)	17.8 (9.6-54.0)	11.1 (4.6-65.5)
Creatinine (mg/dL)	1.4 (0.7-1.6)	0.8 (0.3-1.9)
LDH (U/L)	875 (506-2,346)	1,115 (609-5,000)
β ₂ -Microglobulin (μg/L)	6,152 (4,320-13,621) (n = 4)	5,338 (2,450-11,700) (n = 8)
Ferritin (ng/mL)	2,054 (636-2,417) (n = 4)	779 (57-13,612)

Data are expressed as median (ranges).

ALT, Alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; DRESS, drug reaction with eosinophilia and systemic symptoms; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

*Naranjo score was 0 for “doubtful,” 1-4 for “possible,” 5-8 for “probable,” and ≥9 for “definite.”

†Interval from the first day of drug administration to onset of DRESS syndrome-like manifestation.

DRESS syndrome with lymphadenopathy are observed, early lymph node biopsy should be performed to exclude the possibility of AITL.

The low frequency of hepatic dysfunction in AITL can be explained. Hepatic involvement has been reported in 48% of AITL cases¹ and 80% DRESS syndrome cases.⁸ Interestingly, renal impairment was observed more often in AITL; renal

involvement has been reported in 24% of patients with AITL¹ and 40% of patients with DRESS syndrome.⁸ In DRESS syndrome, however, a certain drug, such as allopurinol, may involve kidney more frequently. Our study only included 3 cases of allopurinol-induced DRESS syndrome. We found that the latent period was much shorter in AITL than in DRESS syndrome. DRESS syndrome is characterized by a longer period, typically

2–6 weeks. If the latent period is too short, it may be reasonable to consider AITL rather than DRESS syndrome. Our AITL case 2 was suspected of having DRESS syndrome based on RegiSCAR score, although no blood eosinophilia. A literature study reported that eosinophilia was found in 52% of DRESS syndrome cases.⁸

AITL has a very poor prognosis.³ However, our patients with AITL exhibited even worse prognosis. Median survival time was just 19 days (Table 1). DRESS syndrome—mimicking AITL might behave more aggressively. Variable phenotypes of AITL might exist. In addition, patients with AITL may be susceptible to infection due to immune dysregulation⁹; this might explain the septic complications in our patients. Thus, earlier diagnosis is required in patients with DRESS syndrome—mimicking AITL. However, whether or not earlier diagnosis affects AITL prognosis is unknown because the rarity of AITL might limit studies on prognostic factors.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication September 9, 2018; revised November 29, 2018; accepted for publication November 30, 2018.

Available online December 14, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.11.048>

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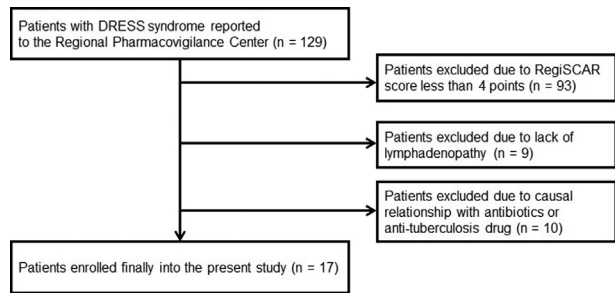


FIGURE E1. Procedure for recruiting patients with DRESS syndrome with lymphadenopathy. RegiSCAR scores were used to assess the diagnostic probability of DRESS syndrome; the score was <2 for “no case,” 2-3 for “possible,” 4-5 for “probable,” and ≥6 for “definite.” Antibiotic- or antituberculosis drug-associated DRESS syndrome cases were excluded because lymphadenopathy might have been caused by bacterial or tuberculosis infection itself. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *n*, number of patients; *RegiSCAR*, European registry of severe cutaneous adverse reactions.

TABLE E1. Comparison of lymphadenopathy, hepatomegaly, and splenomegaly occurrence between angioimmunoblastic T-cell lymphoma and DRESS syndrome cases

CT findings	Angioimmunoblastic T-cell lymphoma (n = 5)	DRESS syndrome (n = 17)
Lymphadenopathy		
Maximal LN width (cm)		
Neck	1.0 (1-1.6) (n = 4)	0.9 (0.5-1.5) (n = 9)
Chest	1.6 (1-1.8)	0.9 (0.6-1.3)
Abdomen	1.4 (1.3-1.8)	1.1 (0.5-1.8)
Number of abnormal LN ≥ 10, n (%) [*]		
Neck	4 (100) (n = 4)	5 (56) (n = 9)
Chest	5 (100)	7 (41)
Abdomen	5 (100)	9 (53)
Hepatomegaly, n (%) [†]	0 (0)	2 (12)
Splenomegaly, n (%) [‡]	5 (100)	6 (35)

Data are expressed as median (ranges).
CT, Computed tomography; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *LN*, lymph node.
^{*}Abnormal lymph nodes were defined as intranodal necrosis or increasing short axial diameter of more than 1 cm.
[†]Hepatomegaly was defined as midclavicular hepatic length >14 cm on coronal reformat of an abdominal CT scan.
[‡]Splenomegaly was defined as a length of >12 cm measured from the superior to the inferior pole of the spleen on coronal reformat of an abdominal CT scan.

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