J Med Sci 2017;37(3):113-116
DOI: 10.4103/jmedsci.jmedsci_61_16

CASE REPORT

A Fatal Case of Drug Reaction with Eosinophilia and Systemic Symptom Syndrome Associated with Cytomegalovirus Reactivation

Yu-Hsiu Chen[1], Shun-Neng Hsu[1,2], Yu-Lueng Shih[1,3], Tsai-Yuan Hsieh[1,3]

[1]Department of Internal Medicine, National Defense Medical Center, Tri-Service General Hospital, [2]Department of Internal Medicine, Division of Nephrology, Tri-Service General Hospital, [3]Department of Internal Medicine, Division of Gastroenterology, National Defense Medical Center, Tri-Service General Hospital, Taipei, Taiwan, ROC

Drug reaction with eosinophilia and systemic symptom (DRESS) syndrome is a severe adverse drug-induced reaction. Diagnosing DRESS syndrome is also challenging due to the diversity of cutaneous eruption and the organs involved. Here, we described an 88-year-old Chinese woman who developed DRESS syndrome under combined therapy of nonsteroidal anti-inflammatory drugs (NSAIDs) and chlormezanone (CM) accompanied with cytomegalovirus reactivation. DRESS syndrome should be highly suspected in patients with symptoms, including skin rash, fever, liver involvement, hypereosinophilia, and lymphadenopathy, especially coexisted with reactivation of the cytomegalovirus. Early withdrawal of the culprit drug is necessary once the diagnosis is established.

Key words: Acute pancreatitis, chlormezanone, drug reaction with eosinophilia and systemic symptom syndrome, drug reaction, eosinophilia, liver decompensation, multiple organ failure, nonsteroidal anti-inflammatory drug

INTRODUCTION

Drug reaction with eosinophilia and systemic symptom (DRESS) syndrome is a severe adverse drug-induced reaction that usually presents clinically as an extensive skin rash, accompanied by fever, lymphadenopathy, hepatitis, hematologic abnormalities with eosinophilia and atypical lymphocytes, and may involve multiple organs.[1,2] Early identification of this syndrome is of particular importance since the mortality rate can reach 10% and the possible persistence or aggravation of symptoms can occur despite the discontinuation of the culprit drug.[3] The drugs most frequently associated with the development of DRESS syndrome are carbamazepine and allopurinol; although, up to 50 drugs induce DRESS syndrome.[4]

We report a case of an 88-year-old Chinese woman who developed DRESS syndrome with liver decompensation and acute pancreatitis as well as cytomegalovirus (CMV) reactivation under combined therapy of nonsteroidal anti-inflammatory drugs (NSAID) and chlormezanone (CM). DRESS should be considered in patients with symptoms including skin rash, liver involvement, fever, and hypereosinophilia. It also stresses the importance of awareness of this rare and lethal adverse effect and evaluation of CMV reactivation while aggravated symptoms with a reduction of leukocyte count.

CASE REPORT

An 88-year-old woman presented to our hospital with fever, poor appetite, and generalized skin rash for the past 3 days. The skin rashes first appeared on the face, and then spread to the upper extremities, trunk, and lower extremities. Thirteen days before presentation, she took etodolac 200 mg and CM 100 mg twice a day for 3 days.

She had chronic kidney disease (creatinine, 1.5 mg/dl), hypertensive cardiovascular disease, and left femoral neck fracture postsurgery 6 years ago, no prior liver disease, and

Received: July 08, 2016; Revised: March 01, 2017; Accepted: March 17, 2017
Corresponding Author: Dr. Tsai-Yuan Hsieh, Department of Internal Medicine, Division of Gastroenterology, National Defense Medical Center, Tri-Service General Hospital, 325, Sector 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan, ROC. Tel: +866-2-87927409; Fax: +866-2-87927139. E-mail: tyh1216@ms46.hinet.net

How to cite this article: Chen YH, Hsu SN, Shih YL, Hsieh TY. A fatal case of drug reaction with eosinophilia and systemic symptom syndrome associated with cytomegalovirus reactivation. J Med Sci 2017;37:113-6.

no prior allergic history to flurbiprofen or other NSAIDs. On physical examination, fever up to 38.5°C, facial edema, yellow sclera, and generalized itchy maculopapular exanthema all over the body were found. There was no peripheral lymphadenopathy. Laboratory data are shown in Table 1. Abdominal ultrasonography and a computed tomography scan showed normal liver size and gallbladder stones (1.9 cm in size) without wall thickening. Transthoracic echocardiography showed normal left ventricular systolic function and ejection fraction was 60%.

The combined therapy of CM and etodolac was stopped 10 days before admission. She was started on ceftriaxone 2 g intravenous once a day following growth of *Escherichia coli* in urine culture. Blood cultures were sterile. The patient became afebrile and the eosinophil count returned to a normal value after 5 days. However, diffuse erythematous confluent macules and patches with scales over the whole body [Figures 1 and 2] worsened even when treated with intravenous betamethasone. Serum urea (109 mg/dl), creatinine (2.4 mg/dl), amylase and lipase (245 and 469 IU/L), total and direct bilirubin (15.6 and 14.5 mg/dl), and liver enzymes (457 and 1069 IU/L) were gradually elevated during the follow-up. Thrombocytopenia (platelet, 40,000/mm^3) and pancytopenia (hemoglobin, 7.9 g/dl; white blood cell, 3470/mm^3; and platelet, 13,000/mm^3) were noted by the 10th and 17th day after admission. We performed further blood cultures and polymerase chain reaction (PCR) assays for the detection of herpes simplex virus, CMV, and Epstein–Barr virus (EBV). Anti-CMV IgM antibody and PCR were all positive. A chest X-ray showed bilateral interstitial infiltrates. CMV reactivation with bone marrow suppression and lung involvement were impressed. Hemodialysis and mechanical artificial liver were performed for acute renal failure and liver decompensation. The clinical status of the patient gradually deteriorated. On the 18th day of admission, the patient died of multiple organ failure. The patient was diagnosed with DRESS syndrome as defined by the two diagnostic criteria, the RegiSCAR criteria, and the Japanese consensus group criteria.

Table 1: Laboratory data

	Value	Normal range
White cell count (/mm^3)	7.53	4.50-11.00
Hemoglobin (g/dl)	10.5	12.0-16.0
Platelet count (/mm^3)	162	150-400
Eosinophils (%)	14.7	0.0-7.0
Alanine aminotransferase (U/L)	187	41
Aspartate aminotransferase (U/L)	124	40
Gamma-glutamyl transpeptidase (U/L)	11	5-36
Alkaline phosphatase (U/L)	47	35-104
Lactate dehydrogenase (U/L)	143	135-225
Urea nitrogen (mg/dl)	36	6-20
Creatinine (mg/dl)	2.2	0.5-0.9
INR	1.3	-
Total bilirubin (mg/dl)	3.8	-1.2
Direct bilirubin (mg/dl)	3.2	
IgE (IU/ml)	89.6	−165.0
Lipase (U/L)	454	13-60
C-reactive protein (mg/dl)	1.80	0.00-0.50
HBsAg	Negative	
Anti-HBc IgM	Negative	
Anti-HCV	Negative	
Anti-HBs	Positive	
Antinuclear antibodies	Negative	
Weil-Felix test	Negative	
HSV-IgM	Negative	
EBV VCA IgM	Negative	
CMV-IgM	Positive	
CMV-PCR	Positive	

INR=International normalized ratio; HBsAg=Hepatitis B surface antigen; HBc=Hepatitis B core; HCV=Hepatitis C virus; HBs=Hepatitis B surface; HSV=Herpes simplex virus; EBV=Epstein-Barr virus; VCA=Viral-capsid antigen; CMV=Cytomegalovirus; PCR=Polymerase chain reaction

DISCUSSION

CM is a widely prescribed muscle relaxant which has been reported to cause Stevens–Johnson syndrome, toxic epidermal necrolysis, and fulminant hepatitis.[5] Etolodac is a NSAID, the culprit drug in DRESS syndrome. She was diagnosed as DRESS syndrome caused by the CM and etodolac due to (1) the close relationship between the initiation of CM and etodolac and the onset of symptoms, (2) the elimination rate

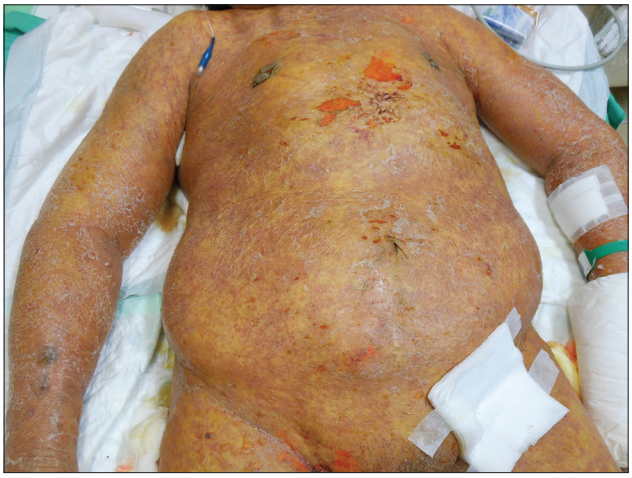

Figure 1: Whole body of the patient showing diffuse erythematous confluent macules and patches with scales

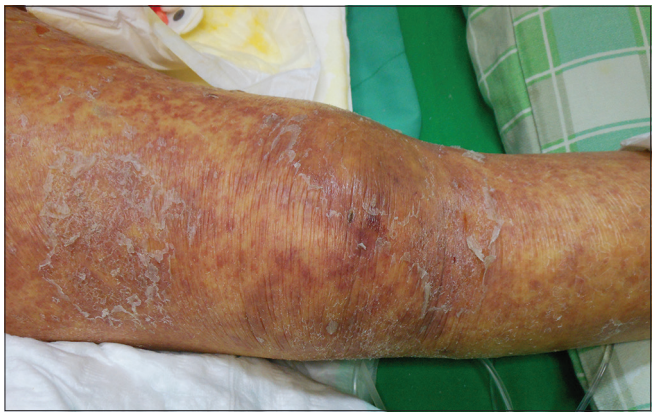

Figure 2: Right knee of the patient showing erythema and exfoliation

of CM and etodolac in elderly patients are reduced related to the reduction in renal function and aging,[6] (3) the risk of acute nephrotoxicity of NSAIDs increases with age,[7] (4) fever, (5) skin rash with facial edema, (6) typical laboratory tests included the presence of eosinophilia and atypical lymphocytes, (7) a positive finding of CMV infection which is associated with the development of DRESS, (8) multiple organ involvement including the liver, kidney, lung, and pancreas, and (9) persistent and worsening symptoms after withdrawal from the causative drug. On consideration of the overall findings and using the RegiSCAR scoring system for grading DRESS syndrome cases, we recorded a score of 6 points for this, which is classified as definite DRESS syndrome.

DRESS syndrome is a severe adverse drug-induced reaction. Diagnosing DRESS syndrome is challenging due to the diversity of cutaneous eruption and the organs involved.[1] Life-threatening multiple organ failure has been documented in DRESS syndrome; it carries a mortality rate of about 10%.[8-10] However, no predictive factors for serious cases have yet to be found.

A delayed onset of symptoms 2–6 weeks after the initiation of the causative drug is a feature of DRESS syndrome. The pathogenesis is related to specific drugs, especially aromatic anticonvulsants, altered immune response, sequential reactivation of the human herpesviruses, and association with human leukocyte antigen alleles.[2] The human herpesviruses reactivation such as human herpesvirus (HHV)-6, HHV-7, EBV, and CMV reactivation may stimulate proliferation of both viral-specific and nonspecific CD4 and CD8 T-cells, triggering massive cytokine release, and causing a hypersensitivity reaction.[11] CMV disease is usually seen in immunocompromised patients with HIV infection or postorgan transplantation under immunosuppressant. It rarely develops in immunocompetent individuals. DRESS syndrome is associated with HHV-6 and CMV reactivation. HHV-6 DNA and CMV DNA may be detected in serum 3–5 weeks and 4–8 weeks, respectively, after onset of DRESS syndrome.[12,13] The CMV disease may involve the skin, gastrointestinal tract, lung, and hematopoietic system. Cutaneous CMV disease presents skin lesions with erythematous change and scratch rash. The gastrointestinal tract CMV disease reveals slow bowel movements and shallowed ulcers on endoscopic examination.[13] The image findings of CMV pneumonitis include ground glass opacities, consolidation, or interstitial pattern. The decrease of leukocyte counts may suggest the onset of CMV disease. Confirmation of CMV organ-specific disease needs biopsies for histological examination. Unrecognized CMV disease may deteriorate the underlying disease. Persistent and aggravated symptoms appear to be more apparent in patients with CMV reactivation concomitant with underlying renal or liver function impairment.

CONCLUSION

DRESS syndrome should be highly suspected in patients with symptoms including skin rash, fever, lymphadenopathy, liver involvement, and hypereosinophilia. Early withdrawal of the culprit drug is necessary once the diagnosis is established. This report stresses the importance of awareness of this rare and lethal adverse effect and the evaluation of CMV reactivation while a patient revealed persistent and aggravated symptoms with a reduction of the leukocyte counts.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, *et al.* The DRESS syndrome: A literature review. Am J Med 2011;124:588-97.
2. 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 2012;87:435-49.
3. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272-85.
4. Hicks C, Gulick RM. Raltegravir: The first HIV type 1 integrase inhibitor. Clin Infect Dis 2009;48:931-9.
5. Sheu BS, Lin CY, Chen KW, Chi CH, Chou NH, Lin XZ. Severe hepatocellular damage induced by chlormezanone overdose. Am J Gastroenterol 1995;90:833-5.
6. Bernard N, Fauvel JP, Pozet N, Ferry N, Cuisinaud G, Haond P, *et al.* Pharmacokinetics of chlormezanone in elderly patients. Eur J Clin Pharmacol 1991;41:603-7.
7. Musu M, Finco G, Antonucci R, Polati E, Sanna D, Evangelista M, *et al.* Acute nephrotoxicity of NSAID from the foetus to the adult. Eur Rev Med Pharmacol Sci 2011;15:1461-72.
8. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, *et al.* Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist? Br J Dermatol 2007;156:609-11.
9. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol 2007;156:1083-4.
10. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. Dermatol Online J 2002;8:5.
11. Shiohara T, Kano Y, Takahashi R. Current concepts on the diagnosis and pathogenesis of drug-induced hypersensitivity syndrome. JMAJ 2009;52:347-52.
12. Seishima M, Yamanaka S, Fujisawa T, Tohyama M, Hashimoto K. Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. Br J Dermatol 2006; 155:344-9.
13. Asano Y, Kagawa H, Kano Y, Shiohara T. Cytomegalovirus disease during severe drug eruptions: Report of 2 cases and retrospective study of 18 patients with drug-induced hypersensitivity syndrome. Arch Dermatol 2009;145:1030-6.